MODERN SYNTHETIC STUDIES OF ORGANOSTANNANE REAGENTS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OR PHILOSOPHY

UNIVERSITY OF FLORIDA

2000

To my Mom and Dad,

with all my love and gratitude

ACKNOWLEDGMENTS

I would like to first thank my parents. It was their guidance, love, and unconditional support that made my academic career possible. They have never stopped showing how much they believe in me, and I will be forever grateful.

Next, I would like to thank Eric Enholm for being a dedicated teacher. He created an environment in the lab that encouraged independent thought and creativity, but at the same time provided help and guidance. I believe that Dr. Enholm genuinely cares about his students. He was a great source of support and encouragement for me. I would also like to extend my thanks to Dennis Wright, Tomas Hudlicky, and Merle Battiste for sharing their expertise and wisdom.

Special thanks go to the members of the Enholm research group, past and present. Paul Whitley, John Jia, Kelley Moran and Jim Schulte III provided a great learning and entertaining environment. Thanks also go to Ashwinn Bharadwaj, Aarti Joshi, and Florent Allais, Buck Batson, Ed Whittle, and Ravi Orugunty for making time in the lab very enjoyable. I would especially like to acknowledge Jennifer Cottone for being the crazy bird that she is and making the last few years extremely memorable.

I thank my brothers, Frank and Michael, for their unending amusement and special friendships. I am also very grateful to Nathan Newport for being a constant pillar of love and encouragement , and for making these last few years extraordinary.

Lastly, I would also like to thank my undergraduate research advisor, Alice Deckert, for being a tremendous role model, and for introducing me to the stipulations, frustrations, and mystery of research, and making me love it.

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Of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Philosophy

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By

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December 2000

Chairman: Eric J. Enholm
Major Department: Chemistry

New methods of organostannane chemistry have been examined. Two different polymer supports have been developed which include soluble polystyrene polymers and soluble polymers derived from Ring Opening Metathesis Polymerization (ROMP). The soluble polystyrene was utilized both as a reagent and as a support for alkyl halides. ROMP polymers were used as a support for various alkyl halides. Mechanistic and synthetic studies were also conducted to examine a free radical approach to a [3,3] sigmatropic rearrangement.

The use of a soluble polystyrene polymer to support an allyltin reagent was demonstrated. Several examples of allylation with alkyl halides were performed. This

allylstannane reagent behaved regioselectively showing a preference to halides which were next to electron deficient centers. Tin pollution was tested through the use of ICP-MS and was detected at very low levels. The attempted synthesis and reactions of a few analogs of the allylstannane polymer were accomplished which revealed a few limitations of the polystyrene support.

It was demonstrated that the polystyrene functioned well when used as a support for alkyl halides. Various substrates were used and reacted with two forms of allylstannane under a neutral free radical environment. This methodology was also examined asymmetrically with the use of a carbohydrate acting as a chiral auxiliary. Allylations were initially performed off the support and then studied with the combination of the carbohydrate scaffold and the soluble polystyrene polymer.

Ring Opening Metathesis Polymerizations were used to create polymer supports with higher loading capacities. Several new polymer supported alkyl halides were synthesized and studied under free radical conditions.

Finally the mechanism of a [3,3] Claisen rearrangement under free radical media was studied. Two possible mechanisms were considered and efforts were made to verify the existence of radical intermediates utilizing gas chromatography and EPR spectroscopy. The synthesis of other heteroatom analogs of the primary allyl vinyl ether derivative was completed but did not give the rearranged product when the same conditions were applied.

CHAPTER 1
INTRODUCTION

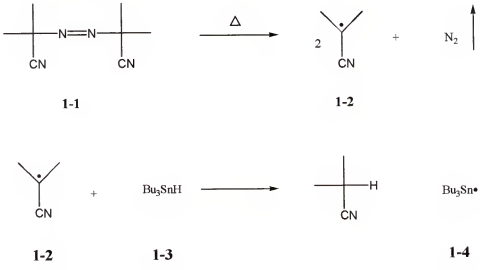
Free Radical Chemistry

The synthesis of organic compounds relies heavily on the formation of carbon-carbon bonds. Free radical reactions have proven to be an invaluable tool for synthesizing carbon-carbon bonds and many other classes of compounds. Carbon centered radicals are made from the homolytic cleavage of a covalent bond. These one electron species are sp^2 hybridized and planar-like carbocations. The atom bearing the radical and its substituents greatly determines the reactivity of the radical.[1] Radicals can either combine with themselves or other functional groups such as olefins, halides, and carbonyls.

There are several distinct advantages for the use of free radicals over ionic media. First, an acidic or basic environment is not required.[2] Free radical chemistry is typically performed in neutral media which protects sensitive chiral centers such as those adjacent to carbonyls from epimerization.[1] Neutral media eliminates the need to use protecting groups for chemically sensitive functions. Also, solvation effects are not present in free radical reactions as they are in ionic chemistry. This is because radicals are not influenced by surrounding polar functional groups and not affected by steric bulk since there is no coordination to other atoms or solvents. For this reason, there is more

flexibility with radicals than with cations or anions because more solvents and hindered functional groups may be used.

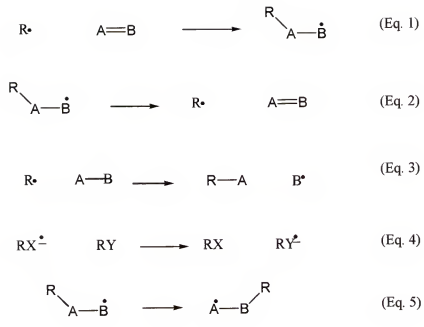
Free radical processes typically undergo chain reactions. Reduction of organo-halides with tributyltin hydride is one of the more commonly used free radical reactions and will be used as an example here. Initiation involves the formation of a one electron species and is usually generated by light or an initiator. Initiators commonly used include dibenzoyl peroxide, di-t-butyl peroxide, t-butyl perbenzoate, and azobisisobutyronitrile(AIBN). Because peroxides have an unstable nature, AIBN **1-1**



1-1 **1-2** **1-2** **1-3** **1-4**

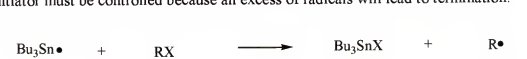
Scheme 1-1

is most commonly utilized. This initiator has a half life of *ca.* 2 h at 80°C and thermally decomposes to give two equivalents of isopropylcyano radicals **1-2** and nitrogen gas as seen in scheme 1-1. Radical **1-2** is a relatively unreactive intermediate although it has the ability to abstract a hydrogen atom from a weak hydrogen bond such as tributyltinhydride. It can also react with a functionalized compound such as allyltributyltin generating the tin radical center **1-4**. Intermediate radical species **1-4** then



Scheme 1-2

participates in a variety of propagation steps as shown in scheme 1-2. The rate of initiation controls the concentration of free radicals in solution. Thus the amount of initiator must be controlled because an excess of radicals will lead to termination.

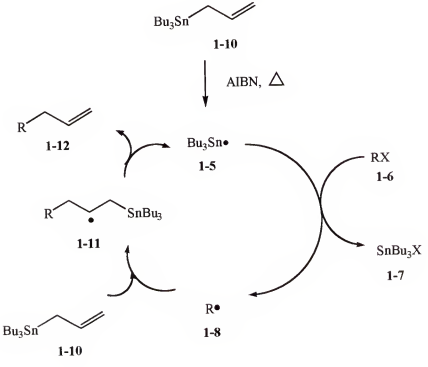


Scheme 1-3

Propagation of the radicals then follows resulting in formation of a new radical species. As shown in scheme 1-2, the propagation steps begin with addition reactions (Eq. 1)

followed by elimination (fragmentation) reactions (Eq. 2), substitution reactions (Eq. 3), electron transfer reactions (Eq. 4), and finally rearrangement reactions (Eq. 5).[1]

In order for a newly formed radical to react with a non-radical compound, two factors must be present: the radical species must have a different reactivity from other radicals present in solution, and the rate of recombination of radicals must be slower than the rate of reactivity of the radical with a non-radical species. Scheme 1-3 demonstrates halide abstraction using a tin centered radical **1-5**. Compound **1-7** is made along with the generation of the alkyl radical **1-8**. This radical **1-8** then abstracts a hydrogen atom from another equivalent of tributyltin hydride **1-3** to regenerate the tributyltin radical **1-5** that continues the propagation steps.



Scheme 1-4

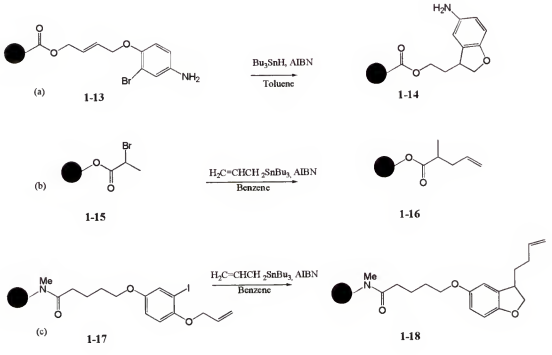
Elimination reactions have proven to be advantageous with the use of allyltributyltin.[1] This reaction involves the formation of an allylated species resulting in the elimination of a trialkyl radical. Scheme 1-4 demonstrates the mechanistic pathway of this allylation. Allyltributyltin **1-10** reacts with the radical initiator AIBN to form the tributyltin radical intermediate **1-5**. This intermediate then reacts with an alkyl halide **1-6** to generate the alkyl radical **1-8** and the tin halide **1-7**. The alkyl radical **1-8** reacts with another equivalent of allyltributyltin **1-10** to form the allylated product **1-12**, and the radical species **1-11** then further undergoes α-elimination to regenerate the tin radical **1-5**.

Free Radical Reactions on Solid Support

The field of radical chemistry applied to solid phase synthesis remains relatively undeveloped considering the number of carbon-carbon bond forming reactions in free radical chemistry. Questions as to whether the polymer backbone would be stable in the presence of reactive intermediates or interfere with such processes are to be addressed in part in this dissertation. Problems with polystyrene have been reported in the presence of organolithium compounds, and with electrophilic aromatic substitution reactions.[3] Polystyrene, due to its reactive benzylic sites, is not useful with these types of reactions.

Some seminal examples of free radical chemistry used on solid support include the following: Routledge and co-workers developed an intramolecular 5-endo cyclization with an aryl bromide as seen in scheme 1-5(a).[4] Hydrogen atom abstraction of compound **1-13** initiated the cyclization rendering product **1-14**. A stoichiometric amount of the radical initiator AIBN was necessary when the resin on **1-13** was polystyrene. When

TentaGel was used, however unusual quenching effects from the polystyrene backbone were evident

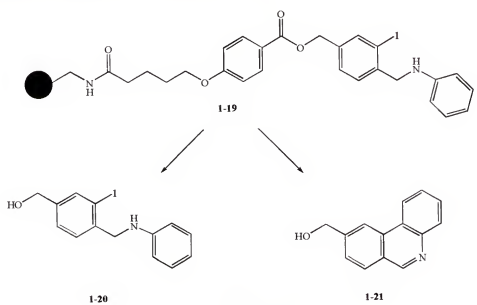


Scheme 1-5

Intermolecular reactions, however are slightly more difficult because of the number of competing reactions that exist especially in free radical media. Early free radical allylations have been reported by Sibi and Chandramouli using solid phase synthesis.[5] α-Bromo esters were mounted on a Wang resin **1-15** as seen in scheme 1-5 (b) and treated with allyltributyltin in refluxing benzene with AIBN used as the initiator. A large excess of AIBN was necessary for this reaction to go to completion and gave the allylated ester **1-16**. De Mesmaeker and co-workers developed a combination of radical

cyclization followed by intermolecular allyltin trapping as seen in scheme 1-5 for compound **1-18** (c).[6]

The De Mesmaeker group used other reactions combining palladium and organotin chemistry with solid phase chemistry.[7] These reactions often have problems associated with purification and would benefit greatly with the facile work-up that solid phase offers. The disadvantage of this method however, lies in the fact that it operates within two phases. Huge excesses of reagents, long reaction times, and harsher conditions are necessary. In scheme 1-6, tributyltin hydride was used to generate a radical cyclization using AIBN as the initiator.[7] Compound **1-19** was treated under these conditions and then cleaved under saponification conditions to render compounds **1-20** and **1-21**. As shown in table 1-1 (entry 4), total conversion of starting material to product was not observed until 16.2 equivalents of tin were used along with 13.5 equivalents of the initiator, normally used in catalytic amounts.



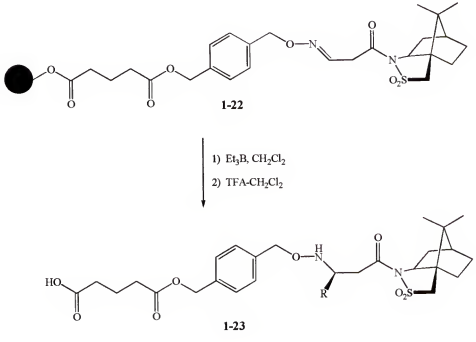
1-19 **1-20** **1-21**

Scheme 1-6

Table 1-1

Entry	Conditions	**1-20**	**1-21**
1	3.6 eq. nBu_3SnH 3 eq. AIBN	74	26
2	7.2 eq. nBu_3SnH 6 eq. AIBN	44	56
3	10.8 eq. nBu_3SnH 9 eq. AIBN	25	75
4	16.2 eq. nBu_3nH 13.5 eq. AIBN	0	100

Naito and co-workers have proven that triethylborane can promote radical reactions on solid support.[8] Even at temperatures as low as –78°C, triethylborane was shown to act as a radical initiator, a Lewis acid, and a termination reagent.



Scheme 1-7

An oxime ether was mounted onto the polymer support with Oppolzer's camphorsultam used as an auxiliary as seen by compound **1-22** in scheme 1-7. Triethylborane was added which resulted in the addition of an ethyl radical and the compound was then cleaved from the support through hydrolysis to give **1-23** in good yield with >95% diastereoselectivity.

Soluble Polymers Used in Organic Synthesis

The emergence of high-throughput screening created a great need from the industrial community for the production of a large number of compounds to be tested for biological activity.[9] For this reason, organic chemists have searched for ways to accelerate the process of small molecule synthesis. This demand is being met by the evolution of combinatorial and parallel synthesis. Combinatorial chemistry has become an invaluable tool to the drug discovery process because it has combined standard solution phase chemistry with efficient purification techniques.[10,11] Chemists have now used techniques from peptide chemistry that use polymers as reagents or as supports. The main benefits include an expedient separation of the substrate from byproducts or excess reagents, and favorable bulky properties that allow for operation in automation equipment.

The most common polymer supports used are ones that are insoluble in organic solvents.[12] These polymers can be isolated by filtration and purified by washing with solvents. Because a biphasic system uses a solid insoluble support and soluble reagents, difficulties arise with attempts to use solution phase conditions. The determination of the

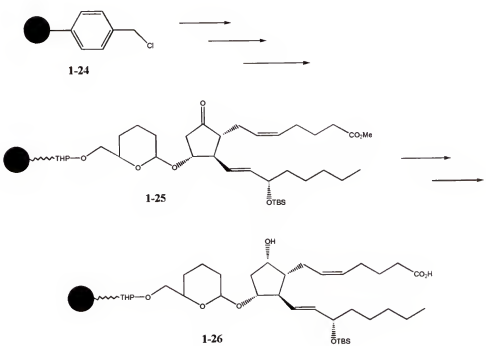
purity of the product and the completeness of the reaction is not possible until the substrate is cleaved from the polymer support.[13]

Soluble polymer support allows for the benefits of solid phase to be combined with the cognizance of solution phase chemistry. These supports offer familiar kinetics and a facile characterization with the benefit of an efficient purification.[13] Numerous forms of soluble supports have been used which include non cross-linked polystyrene, polyethylene glycol, polyacrylic acid, cellulose and polyacrylamide.[14] This dissertation will focus mainly on non cross-linked polystyrene and a newer soluble polymer support we designed which was derived from Ring Opening Metathesis Polymerization(ROMP).

Non Cross-linked Polystyrene

More monomers are amenable to free radical polymerizations than to cationic or anionic polymerizations.[15] Non cross-linked polystyrene, otherwise known as linear polystyrene, has the extendibility of having higher loading capacities and therefore a greater abundance of functional groups on the polymer backbone. When used with a chloro-methyl linker, this polymer support is similar to the Merrifield resin, except that homogenous conditions are utilized. A practical limit is reached however, when the functionalized monomers consist of more than 33% of the polymer backbone. The properties of the polymer begin to change and lose the ability to precipitate well out of polar solvents. Another limitation involved cross-linking of the functional linkers. That is, when the loading capacity reaches a certain limit there is a higher probability of the appended molecules reacting, and in some cases combining. A polymer support solely requires 1-2% cross-linking for the material to become completely insoluble in organic

solvents, so a practical limit of the percent functionality needs to be exercised. These polymers are very soluble in solvents such as THF, methylene chloride, benzene, and ethyl acetate, and are insoluble in polar solvents such as methanol and water. For this reason, precipitation is quite useful from cold methanol. Extraction techniques are also effective with linear polystyrene. This is performed with dilution using methylene chloride or ethyl acetate and washed with any standard aqueous solution.[16] The extra purification capability not possible with common hard resins, is very useful when organometallic chemistry is employed.



Scheme 1-8

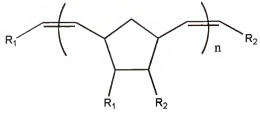
The earliest synthetic application of non cross-linked polystyrene support came from Janda and co-workers three years ago. Although no radical chemistry was performed, Janda and co-workers utilized the soluble polystyrene polymers directed toward the synthesis of prostaglandin derivatives. It was thought that the synthesis of a large number of these analogs would be useful because of the therapeutic value prostaglandins are known to have.[17] The non cross-linked polystyrene was made from a radical copolymerization of styrene and 3 mol% of vinylbenzyl chloride producing a very small loading value of 0.3 mmol/g. As shown in scheme 1-8, the synthesis began with a Williamson ether displacement of chloride **1-24** which was followed by a variety of synthetic steps leading to linear polystyrene supported prostaglandin E_2 methyl ester **1-25** and prostaglandin $F_{2\alpha}$ 1–**26**.[18,19] Coupling strategies using different components of the prostaglandin skeleton were employed that produced a variety of derivatives of this family. A small combinatorial library was further tested for biological activity. Through the parallel synthesis it was found that one compound demonstrated inhibition against a murine CMV growth in NIH 3T3 cells, demonstrating the utility and practicality of soluble polymers when the synthesis of a number of compounds is necessary with a good purification technique.[20]

Ring Opening Metathesis Polymerization

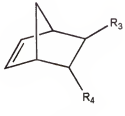
In addition to the non cross-linked polystyrene support, another custom support derived from metal-directed metathesis was examined. Ring opening metathesis polymerization (ROMP) using well-known alkylidene catalysts has proven to be a viable method in the preparation of many polymers.[21] These polymerizations offer the

advantage of incorporating many different functional groups into the polymer backbone, which is difficult to do with vinyl polymerizations. ROMP has been shown to produce a variety of polymeric products such as in the invention of Nylon 6.[22] This method has been developed through the use of new cyclic monomers and catalysts, many of which undergo polymerizations that are cationic, anionic, coordination, and radical mediated.

Polymerizations lead to polymer **1-27** when using a norbornyl substrate such as **1-28**, with the general structure $R_1 M_n R_2$, with M corresponding to the monomer repeating unit and n being the number of repeating units or the degree of polymerization. R_1 and R_2 represent the end groups, the first originating from the insertion of the alkylidene complex and the last from the end-capping agent which is used to terminate the polymerization.



1-27

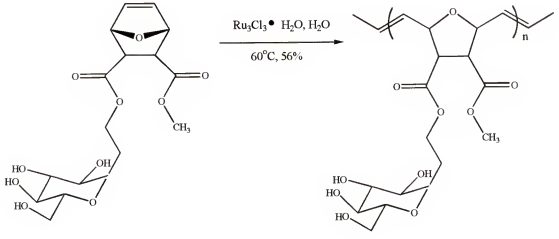


1-28

Figure 1-1

Kiessling and co-workers developed a variety of neoglycopolymers through the use of ring opening metathesis polymerization.[23] ROMP was chosen for its versatility because it provides more control over the size and structure of polymeric materials. It was thought that interactions between protein and carbohydrates may enhance the strength and specificity of cell-cell binding.[24] Polymers containing many carbohydrate

linkages were synthesized to study the effect of multivalent binding on the specificity of protein-carbohydrate interactions. ROMP was favorable because it allows for a highly dense polymer with the capability of occupying one or two sugar linkages per monomeric unit. Monomer unit **1-29** was first synthesized as a mixture of diasteromers. As seen in scheme 1-9, compound **1-29** was polymerized using $RuCl_3$ in degassed water for a period of 12 h. Polymer **1-30** was purified by precipitation in methanol followed by gel filtration chromatography. It was determined that a change in ligand density resulted in an improved binding affinity of a neoglycopolymer for a carbohydrate-binding protein when polymer **1-30** and some derivatives were studied.[23] The ability to change the quantity of reactive sites on the polymer was made possible by the flexibility of ROM polymerization. ROMP allows for an easy method of synthesizing polymers with one or more different ligands in the repeating unit.

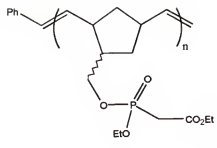


1-29 **1-30**

Scheme 1-9

Ring opening metathesis polymerizations are beginning to be useful to synthetic organic chemists. Polymer supports using ROM have gained acceptance as materials with good properties which allow for a facile purification and high substrate loading. Catalysts commonly used include Schrock's molybdenum alkylidene catalyts Mo(CH-*t*-Bu) (Nar) (OR_2)[25,26] and Grubbs' ruthenium carbenes Cl_2-Ru(CH=CPh_2) $(PyCy_3)_2$ and $Cl_2Ru(CH\text{-}Ph)$ $(PCy_3)_2$.[27,28]

These polymers have been used as reagents to remove unwanted byproducts, as supports, and as chemical reagents. Barrett and co-workers have employed a number of ways to use ring opening metathesis as a support for common synthetic techniques.[29] In one example a Horner-Emmons reagent was mounted directly on the polymer support.[30] The functionalized monomer was used exclusively in the polymerization, creating a high loading capacity. As shown in figure 1-2, two Horner-Emmons reagents were synthesized by ring opening metathesis polymerization using Grubbs' catalyst. The polymer was in the form of a solid but displayed swelling properties with organic solvents such as acetonitrile, methylene chloride, and THF. The polymer was also found to be quite stable at room temperature under an atmosphere of air. The polymerizations were monitored by ^1H NMR spectroscopy in $CDCl_3$ with the vinyl protons having characteristic signals between 5.2-5.5 ppm. When added to a variety of aldehydes with base, polymers **1-31** and **1-32** gave α–β unsaturated esters and α–β unsaturated nitriles with virtually no purification needed.[30]



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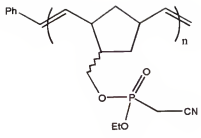


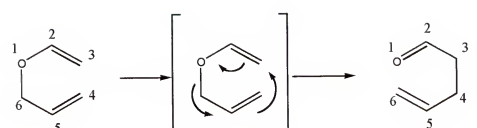
1-32

Figure 1-2

[3,3]-Sigmatropic Rearrangements

The sigmatropic reaction most commonly found in organic synthesis is the [3,3]-sigmatropic rearrangement.[31] This process consists of a concerted, pericyclic reaction that is governed by orbital symmetry. The Claisen rearrangement which was discovered in 1912 is a very useful synthetic transformation that involves a [3,3]-sigmatropic rearrangement of allyl vinyl ethers. The [3,3]-sigmatropic rearrangement is analogous to the cope rearrangement mechanistically except that the product incorporates a carbonyl compound. Scheme 1-10 shows an example of a simple transformation of an allyl vinyl ether **1-33** in which very high temperatures were needed to generate **1-35**.

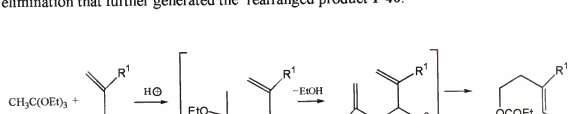
Many variations of the Claisen Rearrangement make this process a very useful synthetic transformation. The orthoester Claisen rearrangement was developed which allows for the rearrangement of an orthoester to a trans-trisubstituted double bond.[32] As



1-33 **1-34** **1-35**

Scheme 1-10

seen in scheme 1-11, a mixed orthoester **1-36** was made which was followed by elimination that further generated the rearranged product **1-40**.

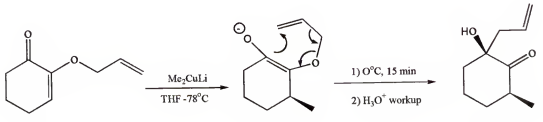


1-36 **1-37** **1-38** **1-39** **1-40**

Scheme 1-11

The discovery of charge accelerated sigmatropic rearrangements led to dramatically improved reaction conditions. The anionic oxy-Cope rearrangement was discovered by Evans and Golob in 1975 and demonstrated a remarkable rate enhancement when catalyzed with base.[33] The reaction was accelerated by factors of 10^{10}-10^{17} which supported Carpenter's theoretical model that states cationic, anionic, and radical substituents may increase the rate of reaction.[34] Breslow and Hoffman explained

this increase by stabilization in the transition state through delocalization of the charge.[35] In accordance with this model, Ireland and Mueller studied lithium enolate derivatives of allyl esters and found an unprecedented rate acceleration for the Claisen rearrangement at lower temperatures.[36] Korreda and co-workers discovered an anionic accelerated



1-41 **1-42** **1-43**

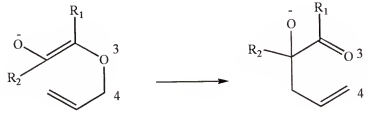
Scheme 1-12

Claisen rearrangement of ketones.[37] Scheme 1-12 illustrates a tandem 1,4 conjugative addition-Claisen rearrangement which started with the formation of the corresponding enolate of **1-41.** Upon addition of lithium dimethyl cuprate **1-42** was formed which then cyclized to **1-43** at 0°C. The cyclization was termed an "anionic oxy-Claisen rearrangement" because of its similarities to the oxy-Cope rearrangement. Evans and

1-44 **1-45**

Scheme 1-13

Golob detected a rate-accelerating effect if an electron donating group (metal alkoxide) was placed in the 3 position of a structure similar to compound **1-44** as seen in scheme 1-13.[33] When the oxy-Cope (scheme 1-13) is compared to the anionic oxy-Claisen (scheme 1-14), the bonds that are formed are in different positions. However, the affects of the donor metal alkoxy group have similar effects on both systems because of the stabilization of the transition state. For the oxy-Cope case, it was postulated that the transition state was stabilized because of the weakened C3-C4 bond. It appears that the anionic oxy-Claisen rearrangement should be explained with the same reasoning due to the position of the oxy anion in conjunction with the bond that is cleaved (scheme 1-14).

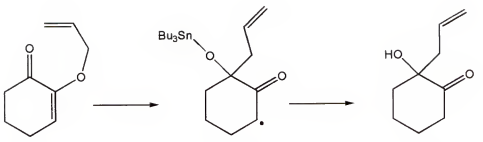


1-46 **1-47**

Scheme 1-14

Electron Paramagnetic Resonance Spectroscopy(ESR)

The mechanism of a radical anion initiated [3,3] sigmatropic rearrangement was studied and will be discussed in this dissertation. In order to detect the existence of radical intermediate **1-49** as seen in scheme 1-15, ESR was utilized. Also known as EPR,



1-48 **1-49** **1-50**

Scheme 1-15

this method of spectroscopy allows for the detection of the energy levels of an electron between two possible orientations of the electron spin.[37] EPR is a very precise method of observing radicals because it only detects unpaired electrons. The spacing of the energy

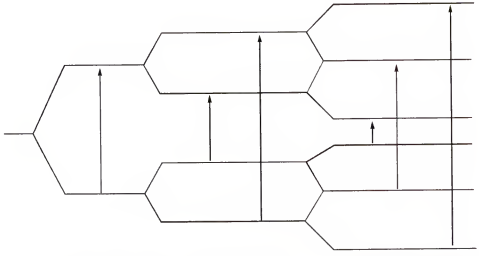


Figure 1-3

levels associated with the transition states are so small that they only correspond to microwaves. EPR works by recording the absorption when an electron makes the transition from a lower state to a higher state. Structural information of a radical intermediate can be assessed when detailed spectra are studied. Hyperfine splitting also gives valuable information about the position of an electron. Hyperfine splitting is very similar to the spin-spin splitting of ^{1}H NMR spectra. The splitting arises from the interaction of the electron with the nuclei of ^{1}H, ^{13}C, ^{14}N, ^{19}F and ^{31}P. The number of lines can be calculated from $2nI + 1$ where I is the nuclear spin quantum number and n is the number of interacting nuclei. For example a single hydrogen next to an unpaired electron will give rise to a doublet because the value of I for hydrogen is ½ . The splitting pattern for the hydrogen nucleus is shown in figure 1-3 . One absorption line is characterized by the first transition where there is no interacting hydrogen nucleus. One interacting hydrogen nucleus, however results in a spectra with two absorption lines, and three interacting hydrogen nuclei will give three lines. Spectra for an electron next to one interacting nitrogen nucleus will give three lines because the nuclear spin quantum number is 1. Values of I for ^{13}C, ^{19}F and ^{31}P are the same as hydrogen and will give a doublet.

New methods in organotin chemistry will be discussed in the following chapters. A newly-developed allyltin reagent on polymer support will be presented in chapter 2. The short synthesis of the reagent will be illustrated. Several examples involving additions to α-bromo esters will also be discussed along with a theory as to why the reagent behaved regioselectively.

T attempted synthesis of a carbon analog of the allyldibutyltin polymer supported reagent will be discussed in chapter 3. Three synthetic approaches will be discussed along with some insights on the difficulty of working with a high density polystyrene backbone.

Free radical chemistry on polymer support will be presented in chapter 4. Various examples of additions of allyltributyltin and a meth-allyltin to the functionalized polymer support will be discussed. Carbohydrates used as chiral scaffolds were also studied in free radical media and the two methods were combined to study asymmetric allylations on polystyrene support.

Ring Opening Metathesis Polymerization(ROMP) as a means to making a soluble polymer support will be discussed in chapter 5. The synthesis of an α–bromo ester on a norbornyl unit will be addressed along with the subsequent polymerization. Several examples of free radical allylation using these ROM polymers will be examined.

The mechanistic study of a new [3,3] sigmatropic rearrangement with a radical anion intermediate will be addressed. Studies involving gas chromatography and EPR will be explained. An investigation as to whether other heteroatom analogs could also undergo the rearrangement under the same conditions as the allyl vinyl ether and their respective syntheses will be demonstrated.

CHAPTER 2
A POLYMER SUPPORTED ALLYLSTANNANE REAGENT

Introduction

The free radical reaction of allyltributyltin with alkyl halides is an excellent and frequently used approach toward the formation of carbon-carbon bonds.[38] As shown in scheme 2-1, the allyl group of **2-1** readily replaces the halide or other homolytic function X of **2-2** under neutral nonpolar conditions to give **2-3**. The reaction is stereoselective and tolerates a variety of functional groups on **2-1**.[39]

2-1 **2-2** **2-3** **2-4**

Scheme 2-1

The disadvantage of using organotin reagents entails the difficulty of separating tin impurities from the desired products. Tin is a heavy metal with mammalian toxicity.[40] Removal of tin byproducts from a synthesis during individual steps in a drug synthesis would be very useful to the pharmaceutical industry. Today there are few methods available which are able to remove excess tin reagents and byproducts efficiently and conveniently.[41] Tedious methods such as those developed by Curran and co-workers

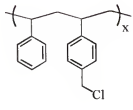
require several attempts of flash chromatography before tin residues are not detectable by NMR spectroscopy.[42,43]

As a step in the right direction, Neumann and co-workers developed a polymer bound tin hydride reagent using an Amberlite XE 305 resin.[44] The cross-linked polystyrene polymer was treated with 1-bromoadamantane under free radical conditions and the reduced product was tested for parts per million of tin pollution . Other polymers bearing an imbedded tin hydride or a tin halide have also been prepared and Table 2-1 shows the amount of tin pollution observed from these early tin polymers. In one case a very high 1975 ppm of tin was released from a support because the iodo-tin side chain underwent β-scission from the resin. These cross-linked resins all have the disadvantage of a labile linkage when applied to mechanical stirring. Vigilant care must be taken when working with these polymers because abrasion of the linker is easily achieved. The number of methylene spacers was increased, prevented β-scission and this resulted in only 34 ppm of pollution.

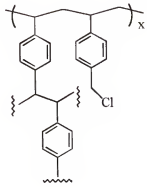
Table 2-1

	SnX/RX molar ratio	Yield % adamantane	Tin Pollution ppm
$P(CH_2)_4SnBu_2I/NaBH_4$	0.9	97	34
$P(CH_2)_2SnBu_2I/NaBH_4$	0.7	70	1975
$Bu_2SnCl/NaBH_4$	0.5	70	15.2×10^4

The use of non-cross-linked polystyrene polymer supports enables the use of traditional reaction conditions without a solid-liquid interface. Complete solubility in THF, ether, hexanes, and other organic solvents allow the reaction to proceed in a single liquid phase environment but with a quick and efficient purification.[45] Unlike the costly cross-linked polystyrene **2-6**, these polymers may be easily made from inexpensive and readily available starting materials. Non-cross-linked polystyrene forms linear polymers that are completely soluble in organic solvents.



2-5



2-6

Figure 2-1

Soluble polystyrene support for liquid phase organic chemistry (LPOC) differs markedly from the standard-2% divinylbenzene cross-linked polymers currently used.[46,47] The number of reactive sites can be controlled from the equivalents of styrene precursors used. Non-cross-linked polymer **2-5** is soluble in organic media, with benefits similar to conventional liquid phase reactions.[48] The rate of the reaction is similar to liquid phase, and the reactions can be monitored by traditional analytical methods such as NMR spectroscopy without cleavage from the polymer support.[45] The main benefit involves the facile purification in each step. The polymers are insoluble in polar solvents such as

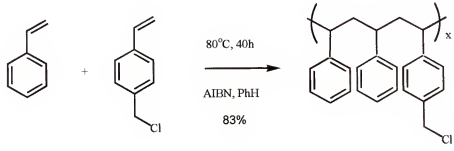
methanol and water so that separation is accomplished through precipitation and filtration. The soluble polystyrene polymers can be obtained as white solids after filtration from cold methanol.

There are two viable approaches available in all polymer-supported methods. The first approach involves attaching the product directly to the polymer so that purification requires only precipitation. The other possibility entails the polymer acting as the reagent. Here a tin reagent can be removed by precipitation and the resulting tin-free filtrate is then concentrated and purified by standard techniques if necessary.

These studies will concentrate on the latter approach where tin reagents will be mounted on the support. Non-cross-linked polymers have never been used to support any tin reagents and we believe these represent the first such examples. Using a polymer support with tin chemistry is useful because there are few methods available which are able to remove tin reagents and byproducts efficiently. One of the goals of this work was to determine if tin impurities could be effectively separated from the product by precipitation. The idea was to synthesize an allyltin reagent mounted on polystyrene support and improve upon the allyltin chemistry first observed by Keck and co-workers.[49]

Synthesis of Polymer Supported Allyltin Reagent

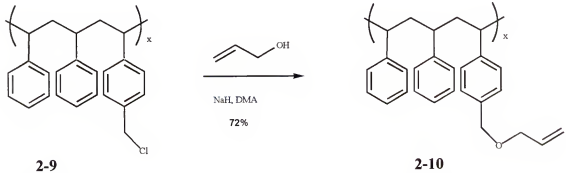
Vinyl benzyl chloride **2-8** was treated with styrene to produce the methyl chloride polymer **2-9** under free radical conditions as shown in scheme 2-2. The conditions were manipulated by varying the equivalents of vinyl benzyl chloride to incorporate more reactive sites into the polymer backbone.[50]



2-7 **2-8** **2-9**

Scheme 2-2

Janda and co-workers have pioneered the use of non-cross-linked polystyrene in synthesis. In most examples of their work, a 10:1 ratio for **2-7**:**2-8** was utilized. Unfortunately, this has a very low loading of 0.3 mmol/per g polymer or a 3% loading



2-9 **2-10**

Scheme 2-3

capacity of the polymer which was used in Janda's recent total synthesis of prostaglandin $F_{2\alpha}$.[47, 51] Although this loading capacity was sufficient for his work, our efforts focussed on maximizing the amount of loading sites on the polymer. A larger loading capacity increases the density of reactive sites on the polymer support and allows for less polymer to be used for every reaction. A study was conducted to explore the maximum loading capacity of this soluble polymer, while still maintaining good qualities of the polymer support such as the ability to precipitate from cold methanol. The optimal range revealed that a 2:1 ratio of styrene to vinyl benzyl chloride functioned best in these experiments balancing the best properties of the polymer with the concentrated number of reactive sites. The non-crosslinked polystyrene polymers were synthesized with increasing amounts of the reactive sites available.

As shown in scheme 2-3, polymer **2-9** was treated with allyl alcohol which produced the corresponding allyl ether **2-10** . The loading capacity was determined by proton NMR integration analysis, and the loading efficiency was calculated.

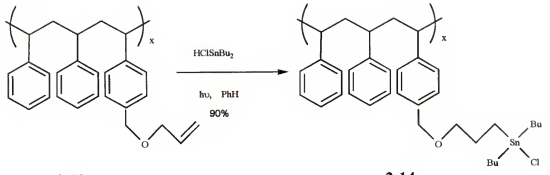
Table 1 illustrates the loading capacities of each polymer which were increased from 3% to 50% of reactive sites available on polymer **2-9**. The near complete displacement by the alkoxide of allyl alcohol (polymer **2-10**) was found to be quite successful and was observed to be independent of the loading capacity. Analysis by ^1H NMR of the central 3-6 ppm region clearly demonstrated the presence of the allyl group in addition to the two methylenes contiguous to the oxygen. The methylene of the benzyl chloride starting material was not observed and was determined to have been consumed in the reaction.

Table 2-2

Loading Capacity	3%	13%	27%	33%	50%
Styrene	32	6.5	3.2	2	1
Vinyl Benzyl Chloride	1	1	1	1	1
Allyl Alcohol % Displacement	>99	93	92	>99	98

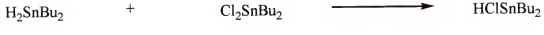
The loading percentage of benzyl chloride and the efficiency of the displacement were carefully observed. Although it is preferred to have a larger loading capacity, a practical limit is reached as the number of reactive sites increases. The structure of the polymer transforms to a gelatinous conformation with increasing amounts of the vinyl benzyl chloride reagent incorporated into the backbone. The polymer thus loses its ability to precipitate well out of cold methanol. Normally the polymer precipitates as a white powder upon filtration; however, this was not the case with increasing incorporation of functional units. It was determined that a 33% loading capacity was ideal because it allowed for the maximum number of reactive sites while maintaining the optimal precipitation properties of the polymer as a white dry solid.

The polystyrene supported allyl alcohol **2-10** was then hydrostannylated as shown in scheme 2-4 using the procedure by Imori to produce polymer **2-14** in 90% yield.[52] The disappearance of the olefin moiety was evidenced by ^{1}H NMR. The reagent dibutyltinhydrochloride **2-13** had to be made fresh from dibutyltindihydride **2-11** and dibutyltindichloride **2-12** as shown in scheme 2-5 and used immediately.



2-10 **2-14**

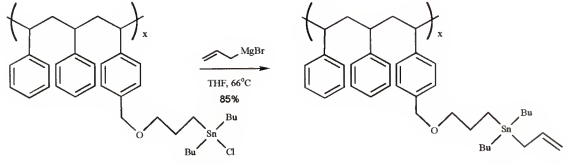
Scheme 2-4



2-11 **2-12** **2-13**

Scheme 2-5

The polymer bound tin halide **2-14** was treated with allyl magnesium bromide which afforded the desired allyldibutyltin polymer **2-15** in 85% yield as evidenced by the appearance of the allyl unit in ^{1}H NMR



2-14 **2-15**

Scheme 2-6

Results and Discussion

Table 2-3

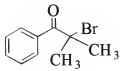
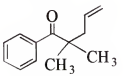
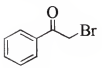
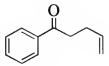
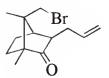
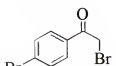
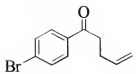
Substrate	Time (h)	Product	Yield
 **2-16**	4	 **2-22**	73%
 **2-17**	12	 **2-23**	73%
 **2-18**	48	 **2-24**	50%
 **2-19**	12	 **2-25**	68%
 **2-20**	12	 **2-26**	66%
 **2-21**	2	 **2-27**	68%

Table 2-3 shows the free radical reaction of polymer **2-15** with a variety of alkyl halides. Substrates containing a bromine atom adjacent to an electron-withdrawing carbonyl group functioned best and gave the expected allylated products. Reactions using standard alkyl halides, such as bromodecane, did not generate any observed products and only unreacted starting materials were recovered. It is interesting to note that no allylated product was reported by Tanner and co-workers for the reaction of α-bromoisobutyrophenone (**2-18**) and allyltributyltin.[53] Using our polymer-bound allylstannane, product **2-24** was obtained in 50% yield. Dihalides in entries **2-20** and **2-21** were regioselective in the free radical allylation producing **2-26** and **2-27** in 66% and 68% yields respectively displaying a strong preference for the electron deficient radical.

It is proposed that polymer **2-15** contains a rather nucleophilic allyltin moiety resulting from an intramolecular interaction with a lone pair of electrons at the ether oxygen atom, as shown in figure 2-2. The oxygen atom may increase the electron density of the tin moiety and make it an electron rich center. The reagent thus may react selectively with electrophilic radical centers.

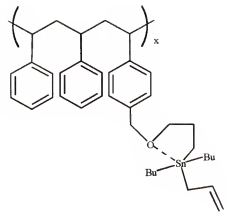


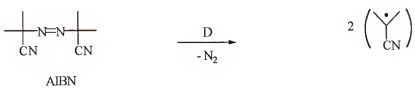
Figure 2-2

The mechanism of the allylation, shown in scheme 2-7, is believed to proceed in the following sequence. First, AIBN **2-27** homolytically cleaves with heat to give two isopropylcyano radicals **2-28**. Tin radical **2-30** is then generated by addition of the allylstannane reagent **2-15** and an isopropylcyano radical **2-28.** An allyltin radical **2-30** may then react with an equivalent of the alkyl halide, R-X to render the tin halide **2-32** and an alkyl radical **2-33**. Another equivalent of the allyltin reagent **2-15** is then coupled with the alkyl radical **2-33** to afford the desired product **2-34** and to regenerate the tin radical **2-30**, then continue the propagation process.

Allylstannane reagent **2-15** on non-cross-linked polystyrene and allyltributyltin were compared for tin pollution in a typical free radical reaction.[54] Bromide **2-19** was reacted with each tin reagent and the allyl product **2-25** in both cases was isolated by column chromatography. Compound **2-25** was dissolved in nitric acid and tested for parts per million of tin using an ICP-MS, and each product mixture was tested twice. The

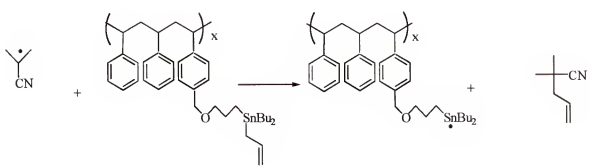
first run gave 6.9 (+/- 0.3) and 53 (+/- 1.0) while the second run gave 15.6 (+/- 0.2) and 79 (+/- 0.7) for the reactions of **2-15** and allyltributyltin.

Initiation



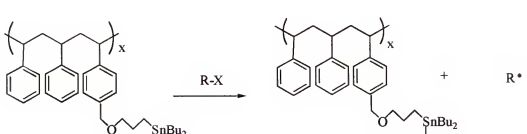
AIBN

2-27 **2-28**

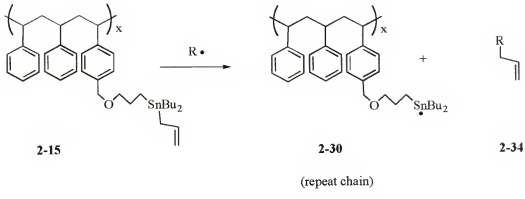


2-29 **2-15** **2-30** **2-31**

Propagation



2-30 **2-32** **2-33**



2-15 **2-30** **2-34**

(repeat chain)

Scheme 2-7

Conclusions

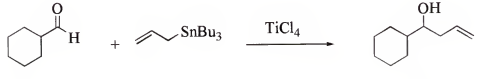
The use of non-cross-linked polystyrene greatly improves the separation of the desired products from tin residue. The polymer support used in these studies has benefits over the standard cross-linked polystyrene, particularly with the ease of monitoring reactions with NMR spectroscopy. Tin compounds and byproducts are readily removed through precipitation and filtration. The allylated products are recovered in good yield with very little tin pollution, as evidenced by ICP-MS. The allylstannane reagent synthesized proved to be regioselective by only reacting with halides next to an electron deficient center. It is believed to be selective due to an interaction between the oxygen atom and the tin atom creating a nucleophilic center and thus preferring to react with electron poor radical center. Regioselectivity was shown when the allylstannane polymer was treated with two examples of dihalides giving the singly allylated products. The

majority of tin pollution was successfully removed as evidenced by the parts per million detected by the ICP-MS.

CHAPTER 3
ATTEMPTED REACTIONS AND SYNTHESIS OF AN ALTERNATE POLYMER SUPPORTED ALLYLSTANNANE REAGENT

Introduction

One of the most useful methods of forming carbon-carbon bonds involves the nucleophilic attack of allyl stannanes to activated aldehydes, ketones and epoxides. Allylstannanes are known to be more reactive than allylsilanes because the carbon-tin bond is weaker and therefore has more anionic character. Tetrasubstituted organotin compounds add directly to these substrates when activated by Lewis acids as shown by Keck and co-workers.[55] For example, addition of allyltributyltin **3-2** to aldehyde **3-1** affords the corresponding homoallylic alcohol **3-3**.



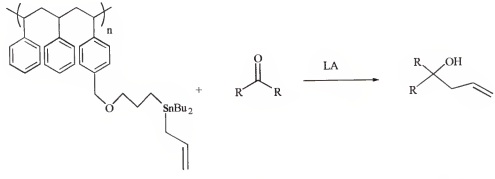
3-1 **3-2** **3-3**

Scheme 3-1

These reactions have also been shown to work without activation of the electrophile. Neumann demonstrated that the addition of allylstannane would occur with only heating.[56]

The most common difficulty with this method is the separation of excess tin reagents and tin impurities from the desired substrates. Soluble polymers such as non-cross-linked polystyrene provide a method that removes tin pollution quite easily.

The first approach was to try a Lewis acid catalyzed reaction using the polymer supported allylstannane reagent previously studied. Scheme 3-2 demonstrates this type of addition reaction on polymer support. It was envisioned that the allyltin reagent



3-4 **3-5** **3-6**

Scheme 3-2

3-4 would add to the activated aldehyde **3-5** and give the homoallylic alcohol **3-6** at the same low temperatures which were used for traditional solution phase.

Results and Discussion

The Lewis acids examined included BF_3OEt, $TiCl_4$, $AlCl_3$, and $Ti(iOPr)_4$. However, the polymer was found to be unstable upon addition of any of the Lewis acids mentioned. The solution became very thick as the form of the polymer transformed from one that was completely soluble in organic solvents, to one that was gelatinous and insoluble in organic and aqueous media. It was believed that the Lewis acid coordinated to the benzyl ether linker of the polymer creating a labile bond as shown in figure 3-1. The resulting cation had the ability to participate in a Friedal-Crafts alkylation with other aromatic rings. This may have resulted in cross-linking which changed the properties of the polymer support irreversibly.[57]

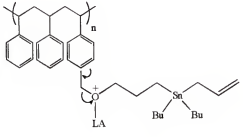
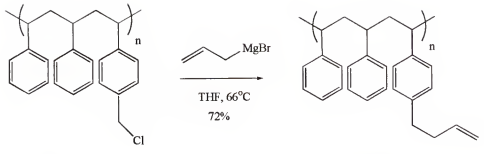


Figure 3-1

It was predicted that a polymer without an oxygen atom would avoid this problem. As shown in scheme 3-3, the soluble chloromethylated polystyrene **3-7**



3-7 **3-8**

Scheme 3-3

was treated with allyl magnesium bromide and gave the butenyl polystyrene **3-8**.

The butenyl polymer **3-8** was then reacted under conditions required for hydrostannylation. Unlike the allyl ether polystyrene **2-10** (see scheme 2-6) which easily hydrostannylated upon irradiation with dibutyltinhydrochloride made in situ, this butenyl polymer did not undergo this reaction. One possibility is that the ether oxygen atom

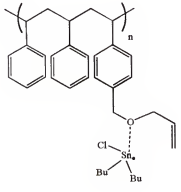
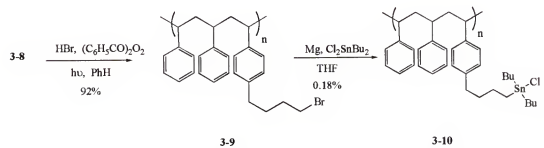


Figure 3-2

aided in the internal delivery of the tin radical to the olefin moiety through a coordination of the oxygen-tin bond as shown in figure 3-2.

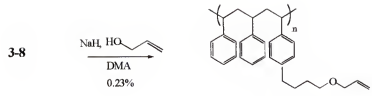
The next attempt at the synthesis of the carbon analog began with the bromination of the soluble olefin polystyrene **3-8**. As shown in scheme 3-4, the olefin was treated with HBr gas in the presence of peroxides to give the soluble brominated polymer **3-9**.



Scheme 3-4

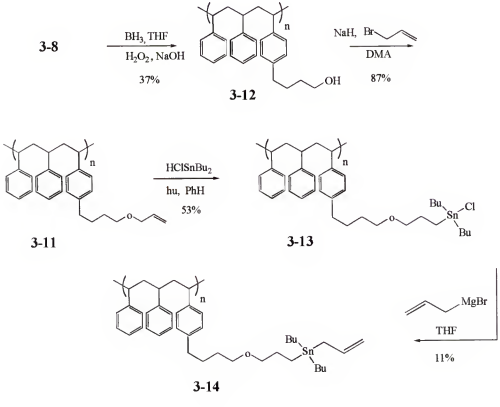
The brominated polymer **3-9** was then reacted with magnesium to generate the Grignard reagent. Further addition of dibutyltindichloride gave the desired tin chloride polystyrene polymer **3-10** with a solid carbon backbone. This reaction proved to be troublesome however with the problem of cross-linking. The majority of the product did not dissolve in organic solvents.

The next option was to synthesize a polymer with an oxygen atom farther away from the benzylic position.[58] The brominated polymer **3-9** was treated with a solution of sodium hydride and allyl alcohol to yield the allyl ether polystyrene **3-11** as shown in scheme 3-5. However, the majority of the product collected was insoluble resulting in a



Scheme 3-5

very low yield. It was believed that cross-linking was again the major obstacle so another synthetic route was designed.

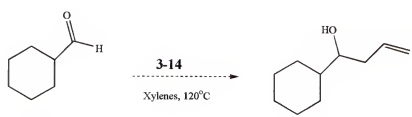


Scheme 3-6

Hydroboration followed by oxidation was performed on the soluble olefin polystyrene polymer **3-8** as seen in scheme 3-6 and gave the alcohol polymer **3-12**. This reaction worked well in that there was no apparent insoluble byproduct. Polymer **3-12** was then treated with sodium hydride and allyl bromide which afforded the allyl ether polymer **3-11**. Hydrostannylation then followed through the use of dibutyltinhydrochloride which gave the tin chloride polymer **3-13**.

The last step in the synthesis involved the use of allyl magnesium bromide. The desired allyl tin soluble polymer with the oxygen moiety further away from the aromatic region was synthesized. Unfortunately this new polymer became insoluble upon addition of the Lewis acid in the presence of an aldehyde.

The reaction was then tested to see if it could be driven thermally. Polymer **3-14** was added to cyclohexanecarboxaldehyde **3-15** in xylenes and the reaction was stirred at reflux for 48 h. There was no homoallylic alcohol product **3-16** observed with this reaction.



3-15 **3-16**

Scheme 3-7

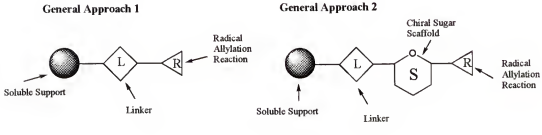
Conclusions

It was the intention of this project to synthesize an alternate allyl tin reagent on polymer support that would be stable in the presence of Lewis acids. The synthesis of a carbon analog of this type of reagent was found to be difficult due to side reactions which made the polymer insoluble in organic solvents. An allyl tin polymer with the oxygen atom farther away from the benzylic system was synthesized, but was also found to be unstable upon addition of Lewis acids. A soluble polymer supported allylstannane reagent which could be used to form carbon-carbon bonds with electrophiles such as aldehydes and ketones would be very useful considering the lack of efficient purification methods involving organotin reagents. Future studies finding a polymer support which would be stable under these conditions is in progress.

CHAPTER 4
ALLYL ADDITIONS UTILIZING SUPPORT AND CARBOHYDRATES

Introduction

Addition reactions of alkyl radicals using allylstannanes are extremely useful methods of forming carbon-carbon bonds. The difficulty with purifying tin compounds however hinders this method from its utmost utility. A variety of methods have been developed to alleviate this problem with little success.[58] As described earlier, the use of soluble supports combined with free radical reactions using allyltributyltin has great synthetic potential. Free radical reactions are not commonly studied compared to the wide array of reactions which have been examined on support.[59] Polymer support allows a means of facile purification between the polymer itself and excess reagents and impurities.[60] Soluble polymer supports dissolve completely in organic media so that



Scheme 4-1

reaction times are comparable to solution phase chemistry.[61] Non cross-linked polymers are insoluble in polar solvents such as methanol and water which allows for an easy

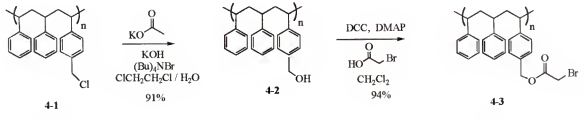
purification through precipitation and filtration. These reactions may also be monitored by traditional analytical techniques such as ^{1}H NMR without cleavage from the polymer backbone. As shown in Scheme 4-1, the non cross-linked polystyrene support was used in two ways: general approach 1 involved soluble supported free radical reactions and linking agents, and general approach 2 included the same polymer support but used carbohydrates as chiral scaffolds to induce asymmetry.

Stereochemical control with free radical media has been a subject of great interest. Sibi[62] and Porter[63] have studied oxazolidinones as a means of chiral auxiliaries under these conditions in the presence of Lewis acids; however polymer supports were not studied. The oxazolidinone moiety is an effective steric bias because of its ability to form a strong chelate with the carbonyl oxygen and the Lewis acid. One focus of this project was to investigate the use of carbohydrates as chiral auxiliaries under free radical conditions. Asymmetric induction using simple sugars is a novel approach for generating stereoselective centers. Carbohydrates are inexpensive and readily available starting materials which have numerous oxygenated functional groups and stereogenic moieties capable of directing stereoselective formation through the use of Lewis acids.[64] Simple sugars serve well as enantiomerically pure precursors because their absolute configuration is known. Carbohydrates have more asymmetric centers than most other classes of compounds[65] and have been used extensively as auxiliaries for the use of asymmetric induction. Charette and Cote developed a method of stereoselective Simmons-Smith cyclopropanation[66] and asymmetric epoxidations using glucose as a chiral template.[67] No attempt was made however to mount this type of reaction on polymer support.

In this project, we attempted to study free radical allylations using soluble supports, carbohydrate auxiliaries, and a combination of both in order to attain good stereoselectivity with a facile purification.

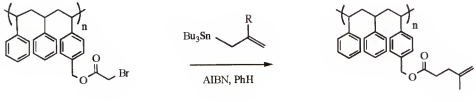
Allylations on NCPS

An α-bromo-ester was tethered onto a soluble polystyrene support as seen in Scheme 4-2. The benzyl chloride supported copolymer **4-1** was made from inexpensive



Scheme 4-2

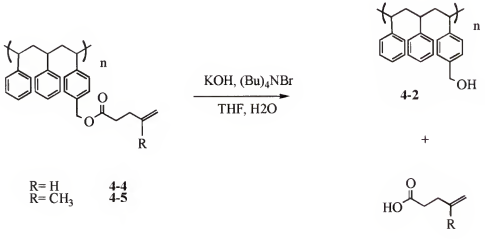
and commercially available styrene and vinyl benzyl chloride.[68] The loading capacity was determined to be 33% by ^{1}H NMR, or 2.7-3.0 mmol/g. The weight average molecular weight was calculated to be 37,275 with a polydispersity of 2.1.



		Yield
R=H	**4-4**	89%
R=CH_3	**4-5**	77%

Scheme 4-3

As shown in scheme 4-2, the chloride polymer **4-1** was converted to a benzyl alcohol support **4-2** through the use of an acetate substitution followed by hydrolysis. The α-bromo ester **4-3** was then prepared by a coupling reaction with dicyclohexylcarbodiimide, dimethylpyridine, and α-bromo acetic acid. Polymer **4-3** was then treated with allyltributyltin and methallyltributyltin under free radical conditions as seen in Scheme 4-3. This provided the corresponding allylated products **4-4** and **4-5** with quantitative recovery of the polymer and complete conversion as determined by ^{1}H NMR. Scheme 4-



R= H **4-4**
R= CH_3 **4-5**

		Yield
R= H	**4-6**	84%
R= CH_3	**4-7**	70%

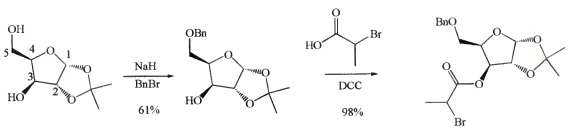
Scheme 4-4

4 shows the allylated esters **4-4** and **4-5** cleaved from the polymer support through hydrolysis to give pentenoic acid **4-6**, and its methyl derivative **4-7** in good yield.

Allylations using Carbohydrates as a Chiral Auxiliary

With this method optimized to remove contamination from organotin compounds, we began to study allylations using simple sugars as a means of asymmetric control. This study was continued from work done by William Batson. A protected form of xylose was chosen for its numerous oxygen sites available to form a strong chelate with Lewis acids.[69] It was reasoned that a C_1-C_2 acetonide could block the α-face oxygens of **4-8** as seen in scheme 4-5. The remaining oxygens at C_3, C_4, and C_5 would be available for a tridentate chelate on the β-face of the ring. An initial concern was that the sugar would be too far from the reacting center and the C_3-carbon would exert no control in the allyl transfer. A second concern was the effect the polymer backbone would have on the diasteroselectivity of the reaction. Finally, it was considered a possibility that cleaving the sugar from the backbone in the presence of strong Lewis acids may be troublesome. This reaction was examined first off of the polymer support because carbohydrates have not been studied as removable chiral auxiliaries for radical reactions.

A bromo propionic ester was attached to a commercially available protected xylose derivative **4-8** as seen in Scheme 4-5. Protection of the primary alcohol as a benzyl ether, followed by a DCC mediated coupling of bromo-propionic acid with the secondary C_3-alcohol afforded compound **4-10** . Treatment of **4-10** with allyltributyltin under free radical conditions produced the allylated ester **4-11** as shown in Scheme 4-6. This reaction was studied using a variety of Lewis acids with the intention of

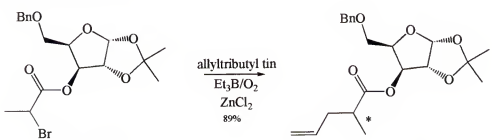


4-8 **4-9** **4-10**

Scheme 4-5

determining which acid provided the best stereoselectivity. Diasteromeric ratios for **4-11** ranged from 7:1 to 12:1 for non-Lewis acid catalyzed reactions. It was assumed that the byproduct tributyltin bromide and/or BEt_3 were functioning as Lewis acids in these reactions. Lower temperatures played a role in increasing the diasteroselectivity.

Zinc chloride proved to be the best Lewis acid, providing a ratio of 28:1. Solubility of the Lewis acids in pure methylene chloride was difficult especially when cooled to −78°C. The diasteroselectivity was successful in most cases although complete conversion of starting material was problematic. 2-methyl-4-pentenoic acid **4-12** was cleaved through hydrolysis.

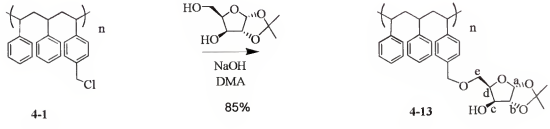


4-10 **4-11**

Scheme 4-6

Allylations using NCPS and Carbohydrate Scaffold Support

The xylose derivative was then tethered to the polystyrene support. This study was continued from work done by Shujun Jiang. Deprotonation of the primary alcohol was completed with an exact measure of 1.1 equivalents of NaH. Any excess of base resulted in an insoluble polymer which may be a result of cross-linking. Addition of the alkoxy sugar to the benzyl chloride polymer **4-1** resulted in the carbohydrate-supported polymer **4-13** as shown in scheme 4-7.

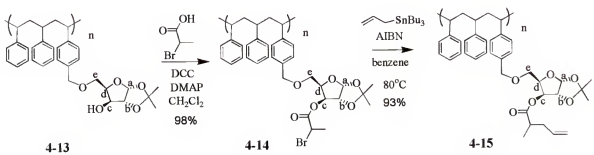


4-1 **4-13**

Scheme 4-7

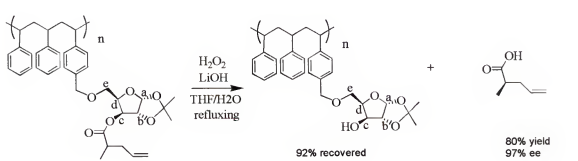
Coupling of **4-13** with α-bromo propionic acid and DCC produced polymer **4-14** shown in scheme 4-8. Some experimental conditions needed to be revised however. The bromo propionic acid and DCC were used in excess, and reaction times were moderately longer. Work-up was standard in that the polymer is separated from any byproducts by means of precipitation and filtration. As shown in scheme 4-8, bromo-ester polymer **4-14** was then

treated with allyltributyltin under free radical conditions which gave allylated ester **4-15**. The loading of the allyl group was not quantitative as it commonly is with these polymers according to ^{1}H NMR. The amounts of allyltributyltin and AIBN were



Scheme 4-8

increased but interestingly, the loading was not affected with an excess of more than five equivalents. From the ^{1}H NMR, it was determined that bromine moiety of polymer **4-14** was consumed but the loading of the allyl group was not quantitative. All attempts to add Lewis acids resulted in cleavage of the sugar from the polymer backbone at the benzyl ether site. Thermal conditions functioned best and the Lewis acid formed was likely



Scheme 4-9

nBu_3SnBr formed during the allylation. Although these conditions are usually not conducive to high diasteroselectivity, it was surprising to obtain good enantioselectivity. The allylated polymer **4-15** was then hydrolyzed as seen in scheme 4-9 to cleave (R)-(-)-2-methyl-4-pentenoic acid **4-12** (97% ee,[70] 80% yield) and recovered polymer **4-9** (92% yield) as a white solid. This reaction needed to be stirred at reflux with an excess of base and peroxide to go to completion.

Conclusions

Non cross-linked polystyrene support provides an improved means of performing free radical allylations without the tedious process of removing organotin byproducts. These allylations have also proven to be stereoselective with the use of a simple sugar derivative as a chiral auxiliary. Carbohydrates have shown to be an excellent source of enantiomerically pure starting materials and supply many sites for chelation with Lewis acids. A commercially available protected form of (D)-xylose was used as a chiral scaffold and was studied independent of the polymer support. It was determined that zinc chloride was the Lewis acid which provided the best diastereoselectivity for the free radical allylation reaction. It was determined that Lewis acid was not effective when this method was mounted on the soluble polystyrene support because of the instability of the linkage under those conditions. High diasteroselectivity was obtained under conditions of reflux with no external acid applied. It was reasoned that the byproduct nBu_3SnBr

may be formed during the allylation. Coupled with the use of carbohydrates as chiral scaffolds, the NCPS methodology provided both a means of asymmetric control with facile purification.

CHAPTER 5
FREE RADICAL REACTIONS ON SOLUBLE POLYMERS DERIVED FROM RING OPENING METATHESIS POLYMERIZATIONS

Introduction

Polymer supported reagents offer several advantages for the synthetic chemist, particularly the ease of handling a large number of compounds with an efficient purification.[71] One of the more common polymer supports, cross-linked polystyrene offers both commercial availability and literature precedence.[72] However, many disadvantages are associated with this resin. Some involve the inability to monitor reactions and the necessity for a large excess of reagents. Another problem is that the loading capacities tend to be rather low. This requires a large amount of the polymer to be used for each reaction in order to obtain a small amount of product after cleavage.[73] High loading with soluble polymers is possible if the monomer unit is exclusively used in the polymerization. This refrains from making a copolymer which normally contains both unfunctionalized and functionalized units. With a homopolymer, the backbone is entirely composed of the monomer unit consisting of reactive sites. These high loading supports then enable a smaller amount of the polymer to be used for each reaction. The interest of this project was to generate high loading resins through the use of ring opening metathesis polymerization for the purpose of allowing for a facile purification of

organotin residues. This also marks the first use of a free radical reaction on any soluble ring opening metathesis polymer support.

Ring Opening Metathesis Polymerization (ROMP) is a transition metal catalyzed polymerization that has found widespread use as a tool for making polymers for material and synthetic purposes.[74] The most common olefin metathesis catalyst, developed by Grubbs and co-workers is the metal-alkylidene complex as shown in figure 5-1.[75] A variety of bridged cyclic olefins have been used to create linear polymers whose backbone contains double bonds linked to a cyclic system. These polymerizations tolerate

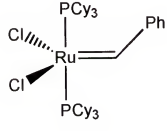
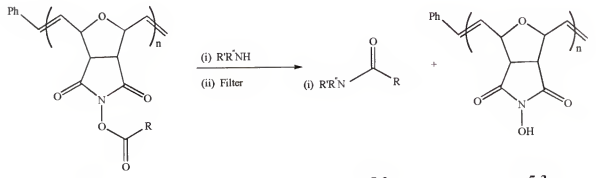


Figure 5-1

a variety of functional groups, generating many possibilities for chemical transformations on polymer support. Ring opening metathesis polymers have been used as organic reagents and as supports for functional group transformations for the purpose of alleviating tedious purifications.[71-73,76] ROM polymers have been commonly used as insoluble polymers, therefore requiring longer reaction times, large excess of reagents, and difficulty in monitoring reactions. As shown in scheme 5-1, Barrett and co-workers developed an N-hydroxysuccinimide polymer **5-1** made from a ring opening metathesis.[2] The polymer was called a "rompgel" on account of its gelatinous consistency and insoluble nature. The polymer reagent was used as an acyl transfer agent. An excess of

the reagent was stirred with a variety of amines to give corresponding amides, carbamates, ureas, Weinreb amides, and hydroxamic acids **5-2**.



5-1 **5-2** **5-3**

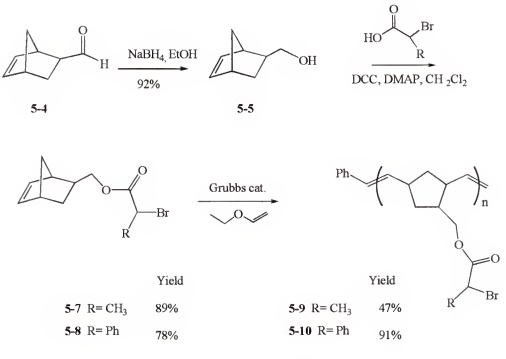
Scheme 5-1

The polymer was recovered and shown to be successfully recycled as the N-hydroxysuccinimide rompgel. The byproducts are usually separated by precipitation or chromatography. There have also been resins developed such as copoly-(ethylene-N-hydroxymaleimide)[77]and a cross-linked polystyrene supported N-hydroxysuccinimide[78]. The ROM polymer derivative was developed however for its superior loading capacity, stability, and increased reactivity.

Some of the ROM polymers created are insoluble in organic solvents. The use of soluble supports clearly offer advantages because it behaves almost identically as that of solution phase chemistry. The reaction times are much improved relative to insoluble supports because a single phase is utilized. Moreover, the reactions can be conveniently monitored by standard ^{1}H NMR spectroscopy without cleavage from the polymer

support. This method also offers the advantage of a facile purification, because the polymers are precipitated from methanol and filtered to give white gum-like solids.

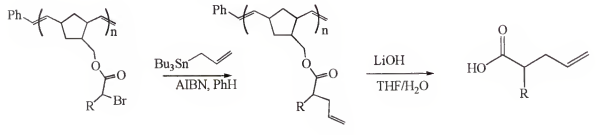
Results and Discussion



Scheme 5-2

A soluble support compatible with free radical reactions was created from ring-opening metathesis polymerizations. Each monomer unit in our designed material contains a functional group, giving every monomer a reactive site integrated into the backbone, or 100 % loading capacity. Scheme 5-2 shows commercially available norbornene 2-carboxaldehyde **5-4** was reduced to give 2-norbornene methanol **5-5**. Coupling of **5-5** with 2-bromo-propionic acid, and 2-bromo-2-phenyl acetic acid in a

DCC coupling gave compounds **5-7** and **5-8** which were carefully purified. Polymerization with Grubbs catalyst created polymers **5-9** and **5-10**. The polymerization of norbornene derivative **5-7** was complete in less than 30 seconds giving **5-9** in 47% yield, which was followed by termination by the addition of ethyl vinyl ether used as an end-capping reagent. The reaction mixture was slowly poured into methanol. It appears that along with the addition of ethyl vinyl ether, polar solvents have the ability to hinder

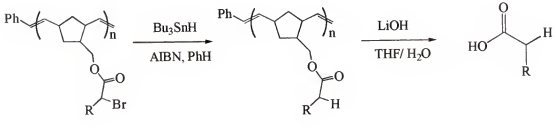


		Yield		Yield
5-9 R= CH_3 **5-10** R= Ph	**5-11** R= CH_3 **5-12** R= Ph	95% 85%	**5-13** R= CH_3 **5-14** R= Ph	87% 76%

Scheme 5-3

the polymerization.[79] A longer reaction time results in a formation of an insoluble gel, which was undesirable. Early termination of the polymerization may limit the molecular weights of the polymers therefore allowing complete solubility in organic solvents. The polymerization of compound **5-8** was improved producing polymer **5-10** in 91% yield after termination with ethyl vinyl ether. It is believed that an improved yield is the result of a longer polymerization time allowing for total consumption of the starting material. If the polymerization time is too long however, the polymer chains increase in length

creating a polymer with properties which does not dissolve well in organic solvents. The gel-like polymer created does possess good swelling characteristics, but requires longer reaction times, an excess of reagents, and does not allow for the ability to monitor the reactions. Purification was accomplished via precipitation in methanol at room temperature. The gum-like solid was removed by filtration and washed with excess methanol. Monitoring of the reactions was conveniently done through the use of ^{1}H and ^{13}C NMR spectroscopy. Scheme 5-3 shows how both α-bromo ROM polymers **5-9** and **5-10** were treated with



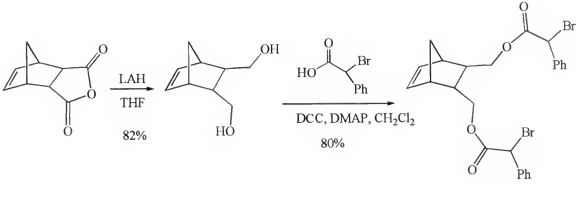
		Yield		Yield
5-9 R= CH_3 **5-10** R= Ph	**5-15** R= CH_3 **5-16** R= Ph	72% 99%	**5-17** R= Ph	59%

Scheme 5-4

allyltributyltin under free radical conditions which afforded the corresponding allylated products **5-11** and **5-12**. The free radical reactions had to be run very dilute with solvent or an insoluble gel-like polymer was created. It is possible that the radical cross-linking of the double bonds within the polymer backbone was responsible.[80] Cleavage of the

allylated esters was accomplished through hydrolysis giving acids **5-13** and **5-14** in good yield. Polymers **5-9** and **5-10** were also reduced with tributyltinhydride as shown in scheme 5-4 under free radical conditions giving the dehalogenated esters **5-15** and **5-16**. ROMP-Supported 2-bromo-2-phenyl acetate **5-16** was cleaved by hydrolysis to give acid **5-17**.

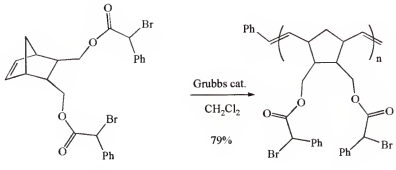
Attention was focused next on further increasing the number of reactive sites for each monomer unit. We next designed two functional groups per monomer doubling the loading capacity of the polymer support. As seen in scheme 5-5,



Scheme 5-5

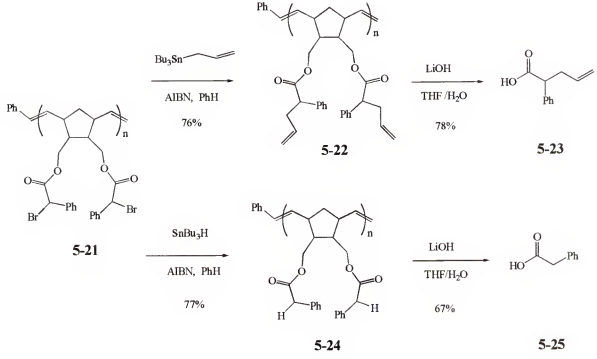
norbornene-2-3-dicarboxylic anhydride **5-18** was reduced with lithium aluminum hydride which gave 5-6-bis-hydroxy methyl norborn-2-ene **5-19**. Coupling with 2-bromo-2-phenyl acetic acid gave the norbornene diester **5-20** in good yield. Polymerization using Grubbs catalyst followed by capping with ethyl vinyl ether afforded polymer **5-21** in 79% yield as shown in scheme 5-6. 2-bromo-2-phenyl ROM polymer **5-21** was treated with

allyltributyltin and tributyltinhydride giving the allylated and reduced polymers **5-22** and **5-24** as shown in scheme 5-7. These ester polymers were then cleaved by hydrolysis affording known acids **5-23** and **5-25**.



5-20 **5-21**

Scheme 5-6



5-21 **5-22** **5-23**

5-24 **5-25**

Scheme 5-7

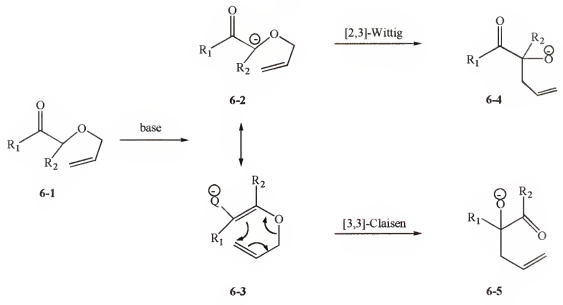
Conclusions

Soluble polymers derived from Ring Opening Metathesis Polymeriztions possess high substrate loading and offer a facile purification with the ease of solution phase chemistry. These soluble ROM polymers possess great handling properties, and can be monitored by NMR spectroscopy. The reaction times are equivalent as that of solution phase, and tin pollution is greatly reduced. To the best of our knowledge, these are the first examples of free radical reactions performed on soluble polymers derived from Ring Opening Metathesis Polymerizations. Efforts are currently under way to apply this support to other free radical processes.

CHAPTER 6
SYNTHETIC AND MECHANISTIC STUDIES OF A KETYL RADICAL-ANION "TRIGGERED" [3,3]-SIGMATROPIC SHIFT

Introduction

Sigmatropic rearrangements have become very significant tools in organic synthesis.[81] One of the most useful rearrangements used is the [3,3]-Claisen rearrangement. This reaction involves the formation of a carbon-carbon bond at the expense of a carbon-oxygen bond. Over the years, attention has focused on improving the method leading to milder conditions and decreased reaction times.[81,82] Charged intermediates have been shown in the literature to accelerate the rearrangement via the use of metal enolates, alkoxides, and silyl ketene acetals.[83] Koreeda and co-workers developed an anionic oxy-Claisen rearrangement through enolates of α-allyloxy ketones.[35] This incorporation of a charge in the intermediate resulted in remarkably lower temperatures and shorter reaction times. α-Allyloxy ketones were studied with a variety of strong bases to generate enolate formation. Scheme 6-1 shows two competing methods of rearrangements. Addition of base to compound **6-1** may rearrange as an α-(allyloxy)α-carbanion, **6-2** and undergo a [2,3]-Wittig rearrangement, or form an enolate as compound **6-3** and carry out the [3,3]-Claisen rearrangement. The two modes were distinguished using different groups for R_1 and R_2.

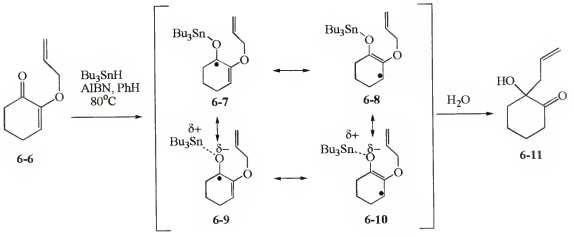


Scheme 6-1

Complete conversion to the hydroxy ketone **6-5** after work-up demonstrated that the [3,3] sigmatropic reaction was the preferred rearrangement.

The use of harsh bases has been avoided through the use of one electron donors such as trialkyltin hydrides. Enholm and co-workers have demonstrated that the Claisen rearrangement may be accelerated by the formation of an allylic O-stannyl ketyl as shown in scheme 6-2.[84] When tin hydrides are added to α,β-unsaturated carbonyl compounds under free radical conditions, allylic O-stannyl ketyls are formed representing the tin(IV) enolate and an allylic radical species.[85] Addition of tributyltin hydride to compound **6-6** under standard free radical conditions rendered the intermediate radicals **6-7** and **6-8**. This ketyl could also be viewed as radical ion pairs **6-9** and **6-10** because of the polarization of the O-Sn bond. The allylic O-stannyl ketyl is a resonance stabilized

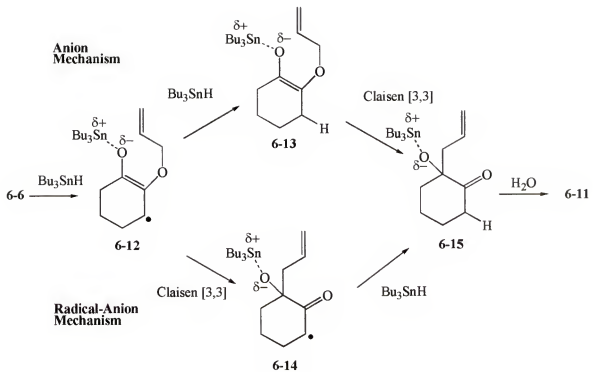
radical that can undergo either anionic or radical reactions. The radical anion was then formed which rearranged to the tin alkoxide giving alcohol **6-11** upon addition of water.



Scheme 6-2

This was believed to be the first example of a radical-anion accelerated Claisen rearrangement. Carpenter's theoretical model has explained that a charged or radical species has the ability to accelerate a sigmatropic reaction by offering stability during the transition state.[86] The allylic O-stannyl enolate intermediate **6-10** contains both radical and anionic character, therefore having the ability to stabilize the transition state. It is possible, but not proven that the presence of the radical may enhance the reaction rate to an even higher degree.

There are two possible mechanistic pathways which lead to the product. Both initially form the intermediate O-stannyl ketyl **6-11**. Scheme 6-3 illustrates both mechanisms where the top pathway indicates the anion mechanism and the bottom explains the radical-anion mechanism. The anion pathway first involves a hydrogen

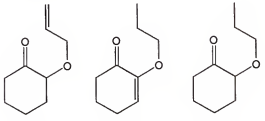


Scheme 6-3

atom transfer which is followed by the [3,3] rearrangement. The radical-anion pathway differs in that the rearrangement occurs before transfer of a hydrogen atom from tributyltin hydride. The first mechanism is unique in that it supports the first radical-anion accelerated rearrangement.[85]

Some mechanistic experiments were devised in order to distinguish between the two mechanisms. The rate of formation of **6-11** and **6-18** were compared starting with **6-6** and **6-17** (as shown in figure 6-1). Both compounds **6-6** and **6-13** could undergo the hydrogen atom transfer, but compound **6-17** lacked the terminal olefin so that the sigmatropic rearrangement was not possible. The rate of formation of **6-18** approximated

the combined rates of allylic O-stanyl enolate formation and hydrogen atom transfer for the anion mechanism pathway. Aliquots were taken from both reactions every 30 minutes and quenched with water. Formation of independently synthesized compound **6-16** was not identified by gas chromatography.



6-16 **6-17** **6-18**

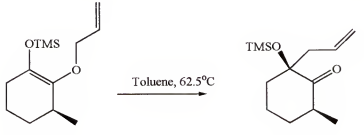
Figure 6-1

This gave support to the radical-anion pathway. In addition, the rate of formation of compound **6-11** was considerably faster than the formation of compound **6-18**. If the anion mechanism were the dominant pathway, then the formation of product **6-11** should have occurred at the same time as reduced product **6-18**.

Mechanistic Studies of [3,3] Sigmatropic Rearrangement

The disappearance of compound **6-6** and appearance of product **6-11** was again studied but at 10 minute intervals for the duration of 3.5 h. For four separate runs with the complete conversion of starting material to product, no detection of compound **6-16** was observed by gas chromatography. If the rearrangement had gone through the anion mechanism, the formation of this compound would most likely be detectable considering

the silyl enol ether derivative **6-19**. Koreeda and co-workers determined the half-life of **6-19** to be 1.6 h during the Claisen rearrangement at 62.5°C to compound **6-20**.[35] Our reaction requires 80°C but detection of the intermediate would likely be expected.



6-19 **6-20**

Scheme 6-4

Furthermore, **6-17** → **6-18** was run under the same conditions and the reaction was determined to be almost an order of magnitude slower than the reaction of **6-6** → **6-11**. Compound **6-17** must follow the first reaction of the anionic pathway because it is missing the terminal olefin and cannot undergo the rearrangement. Both of these studies give strong support to the radical-anion mechanism pathway representing a new mechanistic path for the [3,3] sigmatropic rearrangement.

Because detection of compound **6-13** was not observed, it was important to provide evidence of intermediate **6-14**. This intermediate would not be possible if the reaction went through the anion pathway alone; therefore, evidence was sought for the existence of intermediate **6-14** would further support the radical-anion mechanism. The reaction of **6-6** with tin hydrides was repeated using EPR spectroscopy in order to identify any intervening radical species. This study was performed with the assistance of an Italian collaborator, Angelo Alberti. An argon-purged tert-butylbenzene solution of

compound **6-6** was heated inside the cavity of an EPR spectrometer in the presence of either Ph_3SnH or n-Bu_3SnH, and a small amount of AIBN. In both cases the observed spectra were very similar and exhibited a marked temperature dependence. At higher temperature (T≥353K) as shown in figure 6-3, the spectrum was dominated by a triplet of doublets [$a(1H_\alpha)$ = 1.059 mT, $a(2H_\beta)$ = 1.367 mT, $a(^{217/219}Sn)$ = 1.050 mT, $g = 2.0040_5$]; the central lines of the triplets being somewhat broader and less intense than expected. A weak additional quintet [a(4H) = 1.228 mT, $g = 2.0042_6$] was also observed which was tentatively attributed to the radical anion of cyclohexanone or to the corresponding stannyl adduct.

The spectrum was not consistent with any of the species which might result from addition of stannyl radical to either the carbonyl group or the endocyclic C=C double bond of **6-6**. In fact, for radical **6-12**(figure 6-2) a more complex spectrum would be expected owing to the presence of two pairs of hydrogen atoms in the positions adjacent to the "terminal carbons" of the allylic system, i.e. position 4 and position 6; whereas for the radical resulting from addition to the unsubstituted position of the double bond a single doublet would be expected.

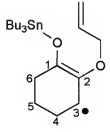


Figure 6-2

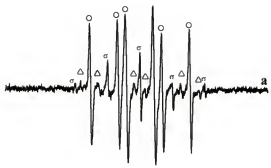


Figure 6-3

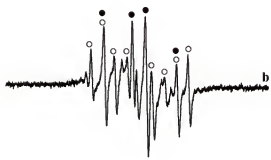
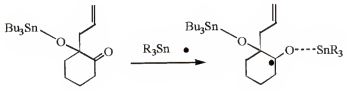


Figure 6-4

On the basis of the spectral parameters, the spectrum(figure 6-3) was assigned to radical **6-14**, where the conformational interchange at 353Kof the six-member ring is "nearly" fast enough to render the two hydrogen atoms adjacent to the allylic carbon in position 4. The spectrum may be interpreted as follows: (O radical **8**; △ Tin satellites of radical **8**; σ cyclohexan-one radical anion; ● radical **13**. Consistently with the previous assignment, as the temperature was lowered to 273K, the triplet became a doublet of doublets [$a(1H_{\square})$ = 0.901 mT, $a(1H_{\square})$ = 0.472 mT and $a(1H_{\square})$ = 2.332 mT] indicating that, although the conformational interchange of the six-member ring is not completely

frozen out, the two hydrogen atoms in position 4 are magnetically unequivalent. The presence of paramagnetic impurities combined with the



6-11 **6-21**

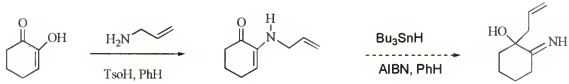
Scheme 6-8

rather low intensity of the spectrum did not allow an accurate kinetic study of the conformational motion of the six-member ring, but there may be little doubt on the identification of radical **6-14**.

As the temperature was lowered, an additional doublet of doublets originating from a different species could also be clearly identified [a(1H) = 1.212 mT, a(1H) = 1.555 mT, g = 2.0040$_0$] as shown in figure 6-4. These signals are tentatively assigned to radical **6-21** as seen in scheme 6-8, most likely resulting from the addition of tin-centered radicals to the reaction product **6-11**.

Synthetic Studies of [3,3] Sigmatropic Rearrangement

The utility of a synthetic method which induces a Claisen rearrangement for an α,β–unsaturated carbonyl compound under neutral free radical conditions is one that would be very useful if exhibite by a variety of functional groups. Attempts were made to see if various amino derivatives, an oxime ether derivative, and a carbon analog would

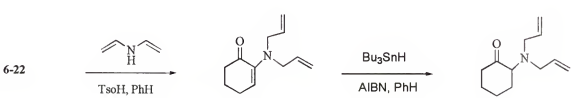


6-22 **6-23** **6-24**

also undergo this rearrangement. The first example included 2-(allyl amino) cyclohexenone **6-23** which was the amino analog of 2-(2-propenyloxy)cyclohex-2-enone **6-6**. The synthesis involved the addition of allyl amine under acidic conditions to 1,2 cyclohexanedione **6-22** which gave **6-23** in good yield. The rearranged product **6-**

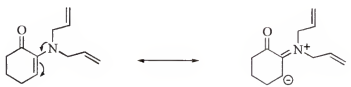
Scheme 6-9

24, however, was not observed. It was thought that the allyl amine may have hindered rotation. An alkylated amine derivative which could not hydrogen bond was synthesized as seen in scheme 6-10 to try to correct the problem.



Scheme 6-10

The diallyl compound **6-25** was made from **6-22** using the same conditions as the single allylated amino compound **6-23**. **6-25** was then treated with tributyltin hydride under free radical media. Unfortunately, the only product isolated was the reduced

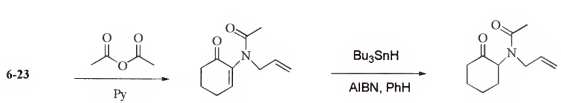


6-27 **6-28**

adduct **6-26**. One theory as to why the rearrangement may be a problem involved the lone pair from nitrogen donating electron density into the system (relative to **6-6**)

Scheme 6-11

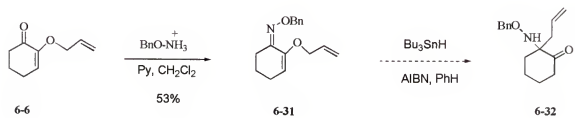
contributing to a resonance system that hinders the rearrangement from occurring. Tin radicals are less likely to add to 6-28 because it is a charged species. Too much negative charge may hinder the addition of the tin radical. Thus compound **6-29** was synthesized from **6-22** which has an electron withdrawing substituent attached



Scheme 6-12

to the amino group to tie up the lone pairs on the nitrogen and avoid resonance structures not conducive to the [3,3] rearrangement. **6-29** was treated with tributyltin hydride under free radical conditions but again,only the reduced product **6-30** was observed.

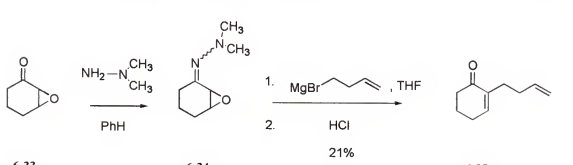
A benzyl oxime ether derivative was next synthesized from compound **6-6** as shown in scheme 6-13. Under free radical conditions with tin hydride, compound



Scheme 6-13

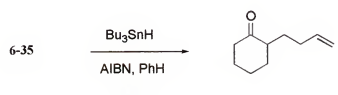
6-31 showed no observable reaction for a period exceeding 12 hours.

A carbon analog was then created starting with epoxide **6-33**. Dimethylhydrazine



Scheme 6-14

was added to give hydrazone **6-34** which was treated with the Grignard reagent of 1,4 bromobutene. The corresponding alcohol was hydrolyzed with acid *in situ* to give enone **6-35**. This compound was then treated with tributyltin hydride in free radical media as seen in scheme 6-15. The reduced cyclohexanone product **6-36** was the only product detected.



Scheme 6-15

Conclusions

Mechanistic and synthetic experiments were used to study a novel [3,3]-sigmatropic rearrangement in neutral free radical media. Studies indicated that the intermediate for the anion mechanism **6-13** was not observed during the reaction giving support to the radical-anion accelerated mechanism. In addition, the rate of reaction of an analog **6-17** which could not undergo the rearrangement but only the hydrogen atom abstraction, was determined to be almost an order of magnitude slower than the reaction

of **6-6** to **6-11**. EPR data was also obtained, detecting a key intermediate in the radical-anion mechanism **6-14** giving further evidence to support this pathway.

Attempts were made with synthesized analogs of enone **6-6** determine if the rearrangement would occur. Derivatives included three amino substituents, a benzyl oxime ether, and a carbon analog. These were synthesized and treated with the same free radical conditions used in the successful rearrangement with **6-6**. No rearranged products were isolated; reduction seemed to be a dominant reaction with the majority of the analogs. The [3,3] sigmatropic Claisen rearrangement under neutral free radical media which avoids harsh basic conditions is a unique and very useful transformation. Future studies on this reaction including an asymmetric rearrangement are in progress.

CHAPTER 7
EXPERIMENTAL

General Methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-300 (300 MHz) spectrometer. Carbon 13 spectra were recorded on a Varian Gemini-300 spectrometer at 75 MHz. Chemical shifts are reported in ppm down field relative to tetramethyl silane as an internal standard in $CDCl_3$. All reactions were run under an inert atmosphere of argon using an oven dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography (TLC) and NMR spectroscopy. Solvents were dried according to established procedures by distillation under inert atmosphere from appropriate drying agents. Analytical TLC was performed using Aldrich Z12272-6 precoated silica plates (0.25 mm) visualizing with UV light (254 nm) or p-anisaldehyde in ethanol with acetic acid as an indicator. Column chromatography was performed using Kieselgel silica gel 60 (230-400 mesh) by standard flash chromatography techniques. GC experiments were performed on a Varian 3500 capillary gas chromatograph using J & W fused silica capillary column (DB5-30W; film thickness 0.25).

Soluble Chloromethylated Polystyrene 2-9

The subsequent procedure was modeled from that of Narita.[2] A solution of styrene (13.6 g, 131 mmol), vinyl benzyl chloride (9.9 g, 65.4 mmol), and AIBN(0.21 g, 1.3 mmol) was stirred in benzene (48 mL). The mixture was degassed with argon for 20 min and subsequently heated to reflux for a period of 40 h. The solution was slowly poured into methanol at –40°C and allowed to cool for a short time. The precipitate was collected by filtration to yield a white solid (19.36 g, 80%). ^{1}H NMR δ 7.3-6.2 (m, H), 4.4 (s, 2H), 2.2-1.2 (m, H). GPC (Mn=17506. Disp=2.129)

Soluble Allyl Ether Polystyrene 2-10

3.21 g of NaH (60% in oil, 80.2 mmol) was stirred in pentanes to remove the mineral oil. 20 mL dimethylacetamide was added to the base, and stirred under argon. A solution of allyl alcohol (4.23 g, 72.9 mmol) dissolved in dimethylacetamide (50 mL) was added slowly, and the mixture was allowed to stir at room temperature for 1 h. The deprotonated allyl alcohol solution was added via cannula to the benzyl chloride polymer (9 g, 24.3 mmol) which was dissolved in dimethylacetamide (65mL). The mixture was stirred at room temperature for 24 h and then slowly poured into cold methanol(78°C). The yellow precipitate was isolated by vacuum filtration (6.66 g, 72%). ^{1}H NMR δ7.3-6.3 (m, 15.53H), 6.0 (m, 1H), 5.1 (m, 2H), 4.4 (s, 2H), 4.0 (m, 2H), 2.2-1.2 (m, 10.3H)

Dibutyltindihydride (2-11)

The following is identical to the experimental procedure of Imori and co-workers.[5] Lithium Aluminum Hydride (3 g, 79.0 mmol) was dissolved in anhydrous ether (200 mL) and cooled to 0°C. A solution of dibutyltindichloride (15 g, 49.4 mmol) and 130 mL dry ether was added dropwise through a cannula. The mixture was allowed to stir at 0°C for 2 h, and then for an additional hour at room temperature. Degassed water (250 mL) was added slowly to quench the remaining LAH. Transfer of the ether layer was accomplished via cannulation to a flask containing calcium chloride. The organic layer was dried for 15 min, and then transferred via cannula to an additional flask. The solvent was removed through reduced pressure to afford the dihydride product (10.89 g, 94%.) Spectral data was identical to that reported by Imori and co-workers.[51] ^{1}H NMR δ 0.85 (t, *J*=7.2Hz, 6H), 0.92 (t, *J*=6.9, 4H), 1.3 (sextet, *J*=7.2Hz, 4H), 1.5 (m, 4H), 4.7 (m, 2H); ^{13}C NMR δ 30.7, 27.1, 13.8, 7.1

Soluble Dibutyltinchloride Polystyrene 2-14

Dibutyltindichloride (3.15 g, 10.4 mmol) and the allyl ether polymer (2.5 g, 6.5mmol) was dissolved in distilled benzene in a pyrex tube filled under an inert atmosphere of argon. Fresh dibutyltindihydride (2.43 g, 10.4 mmol) was added dropwise. The solution was irradiated in a photochemical apparatus for 20 h. The silvery solution was placed under a roto-vap to rid of excess solvent. The mixture was

extracted with ethyl acetate, and washed with water and brine solution. The ethyl acetate was removed under reduced pressure, and the remaining viscous mixture was dissolved in the minimal amount of THF(3 ml), and poured into cold methanol. The gray precipitate was collected through vacuum filtration (3.1 g, 90%). ^{1}H NMR δ 7.3-6.1 (m, 13.84H), 4.3 (s, 2H), 3.3 (m,2H), 2.0-0.7 (m, 55.24H).

Soluble Allylstannane Polystyrene 2-15

A solution of the tin chloride polymer (2 g, 3.6 mmol) dissolved in dry THF was placed under an atmosphere of argon and cooled to O°C. Allyl magnesium bromide (3.12 g, 21.5 mmol) was added dropwise and the resulting solution was stirred at reflux for 8 h. The solvent was removed by reduced pressure and the remaining gray gel-like solution was extracted with ethyl acetate. The organic layer was then washed with water and an ammonium chloride solution. The ethyl acetate was removed through the use of the roto-vap, and the mixture was redissolved in the minimal amount THF necessary. The solution was poured into cold methanol(-40°C), and the white solid was collected by filtration (1.64 g, 85%). ^{1}H NMR δ 7.2-6.2 (m, 11.06H), 5.9 (m, 1H), 4.8-4.6 (m, 2H), 4.3 (s, 2H), 3.3 (s, 2H), 2.0-0.8 (m, 26.1H). GPC (Mn=26663. Disp=2.144)

3-allyl-dihydro-furan-2-one (2-22)

Allystannane polymer (1.5 g, 1.44 mmol) dissolved in the minimal amount of distilled benzene. AIBN (63 mg) and α-bromo-butyrolactone (0.16 g 0.96mmol) was added and the solution was degassed with argon for 20 min. The starting material was observed to be consumed after 4 h by GC analysis, and the mixture was slowly poured into cold methanol. The white precipitate was then separated by vacuum filtration and the filtrate was concentrated under reduced pressure. The crude mixture was then subjected to flash chromatography to afford a colorless oil (87 mg, 73%.) Spectral data was identical in all respects to that reported by Molander and Harris.[87] R_f 0.78 (35% Et OAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 5.7 (m 1H), 5 (m 2H), 4.4 (m, 1H), 4.1 (m 1H), 2.6 (m, 2H), 2.3 (m 2H), 1.9(m, 1H). ^{13}C NMR δ 179.68, 134.23, 117.49, 66.41, 38.62, 34.11, 27.58

3-allyl-3-methyl-dihydro-furan-2-one (2-23)

To a solution of allyltin polymer (1.3 g, 1.9mmol) dissolved in a minimal amount of benzene was added AIBN (30 mg), and α-bromo-butyrolactone (0.14g, 0.83mmol.) The mixture was degassed for 20 min with argon, and was heated to reflux for 5 h. The reaction was cooled to room temperature and subsequent amount of the radical initiator was added(30 mg.) The reaction was once again heated to reflux for an additional 12 h.

Upon cooling to room temperature, the solution was then slowly poured into cold methanol. The white precipitate was isolated by filtration, and the filtrate was concentrated under reduced pressure. The crude yellow oil was then purified by flash chromatography (81 mg, 73%.) Spectral data is identical in all respects to that reported by Toru and co-workers.[88] R_f 0.81 (35% Et OAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 5.6 (m, 1H), 5.0 (m, 2H), 4.1 (t, 2H), 2.1(m, 5H), 1.8 (m, 2H). ^{13}NMR δ 181.53, 132.75, 119.39, 65.02, 42.16, 41.62, 33.72, 22.57

2-2-dimethyl-1-phenyl-4-pentene (2-24)

Allyltin polymer (1.5 g, 2.27mmol) was dissolved in the minimal amount of distilled benzene. AIBN (40 mg), and α-bromoisobutyrophenone (0.14 g, 0.61mmol) were added, and the reaction was heated for 12 h. After cooling to room temperature, another equivalent of AIBN (40 mg) was added and the reaction was further heated to reflux for 12 h. The mixture was then slowly poured into cold methanol (-78°C) and the white solid polymer was separated by isolation. The filtrate was concentrated under reduced pressure and the crude oil was subjected to flash chromatography (57 mg, 50%). Spectral data is identical in all respects to that reported by Barentson and co-workers.[89] R_f 0.91 (35% Et OAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 7.6 (m, 2H), 7.4 (m, 3H), 5.6 (m, 1H), 5 (m, 2H), 2.5 (m, 2H),1.6 (s, 6H). ^{13}NMR δ 208.59, 138.96, 133.96, 130.68, 127.983, 127.51, 118.04, 47.53, 44.86, 25.65

1-phenyl-4-pentene-1-one (2-25)

To a solution of the allyltin polymer (0.85 g, 1.27mmol) dissolved in the minimal amount benzene was added AIBN (21 mg), and 2-bromoacetophenone (0.13 g, 0.636mmol.) The mixture was then degassed for 10 min and heated to reflux for 12 h. The reaction was then cooled to room temperature with a subsequent addition of AIBN (21 mg.) The reaction was heated to reflux for 3 h, and poured into cold methanol(-78°C.) The white precipitate was separated by filtration, and the filtrate was concentrated under reduced pressure. The crude oil was isolated by column chromatography (68 mg, 68%.) Spectral data is identical in all respects to that reported by Yasuda and co-workers.[90] R_f 0.89 (35% Et OAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 7.9 (d, 2H), 7.4 (m, 3H), 5.8 (m, 1H), 5.0 (dd, J=17.09, 1.46 Hz, 1H), 5.01 (dd, J=10.25, 1.46 Hz, 1H) 3.0 (t, J=7.32Hz, 2H), 2.4 (m, 2H). ^{13}NMR δ 199.22, 137.21, 136.84, 132.92, 128.51, 127.95, 115.23, 37.83, 28.25

3-Allyl-7-bromomethyl-1,7-dimethyl-bicyclo[2.2.1]heptan-2-one 2-26

Allyltin polymer was dissolved in the minimal amount of benzene. AIBN(50mg) and 3, 9-dibromo(+)camphor(0.10g, 0.323mmol) was added and the mixture was stirred at reflux for 12 hours. The solution was cooled to room temperature and a further addition of AIBN(50mg) was added. The reaction was then stirred at reflux for 3 hours

and was slowly poured into cold methanol. The white polymer precipitate was then separated by vaccum filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography(57mg, 66%.) R_f 0.78 (35% Et OAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 5.8 (m, 1H), 5.2 (m, 2H), 3.6(d, 1H), 3.2 (d, 1H), 2.5 (m, 1H), 2.4(m, 2H), 1.6(m, 3H), 0.9 (s, 3H), 0.8 (s, 3H). ^{13}C NMR δ 219.5, 135.9, 116.3, 59.4, 48.9, 39.8, 31.4, 30.6, 19.4, 16.6, 9.8, 1.4, 1.0, IR (NaCl) 2952.9, 1740.6, 1638.9, 1447.4, HRMS (EI) calcd for $C_{13}H_{19}BrO$ 270.0619, found 270.0633

4' bromo-4-pentene-acetophenone 2-27

Allylstannane polymer(1g, 1.47mmol) was dissolved in the minimal amount of distilled benzene. AIBN(21mg) and 2, 4'-dibromoacetophenone(0.13g, 0.47mmol) was added and the solution was degassed with argon for 15 min. After stirring at reflux for two hours, thin layer chromatography showed the disappearance of starting material and the mixture was slowly poured into cold methanol(-40°C). The white polymer precipitate was then removed by vacuum filtration and the filtrate was concentrated under reduced pressure. The crude material was dissolved in the minimal amount of ethyl acetate and was then subjected to flash chromatography with hexanes to yield the allylated product(76mg, 68%.) Spectral data is identical in all respects to that reported by Ng and Alper.[91] R_f 0.87 (35% EtOAc/Hex) ^{1}H NMR (300MHz, $CDCl_3$): δ 7.7 (d, 2H), 7.5 (d, J=8Hz, 2H), 5.8(m, 1H), 5.0 (m, 2H), 3.0 (t, J=6Hz, 2H,), 2.4 (m, 2H); ^{13}C NMR δ 198.5, 137.0, 136.0, 132.0, 130.0, 128.2, 112.5, 38.0, 28.0.

Soluble Olefin Polystyrene 3-8

The soluble chloromethylated Polystyrene (10 g, 26mmol) was dissolved in distilled THF and cooled to 0°C. A solution of allyl magnesium bromide was slowly added (104ml, 1M), and the solution was stirred at reflux (66°C) for 12 h. The mixture was then poured into cold methanol (-40°C) and allowed to cool. Vacuum filtration followed by reduced pressure yielded white solid (6.86 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.1 (m, 10.21H), 5.8-5.6 (s, 1H), 5.0-4.8 (m, 2H), 2.7-2.4 (s, 2H), 2.3-2.0 (m, 6.78H).

Soluble brominated Polystyrene 3-9

Soluble olefin polystyrene (5g, 13.5 mmol) was dissolved in the minimal amount of benzene in a glass pyrex tube and was filled with argon. HBr gas was generated through a slow addition of sulfuric acid in an addition funnel(12M) to sodium bromide in a three neck round bottom flask. The gas was bubbled through drierite to the polymer solution for 2 h. The solution was then sealed with argon, irradiated for 12 h, and poured into cold methanol (-40°C). The brown precipitate was collected via filtration to give product (5.02 g, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 22.6H), 3.3-3.2 (s, 2H), 2.6-2.4 (s, 2H), 1.8-1.2 (m, 26.27H).

Soluble Allyl Ether Polystyrene 3-11

Allyl alcohol (0.65 mL, 9.48 mmol) was dissolved in DMA and stirred with NaH (25 g, 10.4 mmol) for 2 h under an atmosphere of argon. The mixture was added to a solution of soluble brominated Polystyrene (1g, 1.58 mmol), dissolved in DMA and stirred under argon for 3 h. The mixture became very thick and appeared to be cross-linked. It was poured into cold methanol (-40°C) and a yellow gelatinous solid was collected through vacuum filtration. The majority of the polymer was not soluble in organic solvents (0.15 g, 0.23%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 32.24H), 5.8-5.9 (s, 1H), 5.2-5.0 (m, 2H), 3.9-3.8 (m, 1H), 3.4-3.3 (m, 1H), 2.5-2.4 (m, 2H), 1.8-1.1 (m, 32.09).

Soluble Tin Chloride Polystyrene 3-10

Soluble brominated polymer (1g, 1.58 mmol) was dissolved in THF and stirred with magnesium metal (0.38g, 15.8 mmol) for 2 h. Solution was added through syringe to a solution of dibutyltindichloride dissolved in THF and was stirred at reflux for 4 h. The solution was then poured into cold methanol (-40°C) and the grey precipitate was collected through vacuum filtration. The majority of the polymer was not soluble in organic solvents (0.2 g, 0.18%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 34.9H), 1.8-0.6 (m, 82.5H).

Soluble Hydroxy Polystyrene 3-12

Soluble olefin polystyrene (1g, 1.3 mmol) was dissolved in THF and BH_3THF(3 mL) complex was added slowly at room temperature. The mixture became very thick within the first hour but eventually became more fluid. After stirring at room temperature for four hours, the oxidation was completed by the addition of 5 ml water, 30ml of 1M NaOH, 25 ml Ethanol and 25 ml H_2O_2. The solution became cloudy and was allowed to stir at room temperature for 2 h. Excess solvent was removed through reduced pressure and the mixture was extracted with ethyl acetate. After washing with water and brine solution, the mixture was again concentrated, and the remaining solid was dissolved in the minimal amount of THF necessary. A white precipitate was collected by filtration after the mixture was poured into cold methanol (-40°C) (0.4 g, 37%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.1-6.1 (m, 44.4H), 3.7-3.4 (m, 4H), 2.6-2.4 (s, 2H), 1.8-1.1 (m, 42.8H).

Soluble Allyl Ether Polystyrene 3-11

Soluble hydroxy polystyrene (0.22g, 0.196 mmol) was dissolved in DMA, and stirred with NaH (0.11g, 2.94 mmol) at room temperature under argon for 1 h. Allyl bromide (0.4g, 3.92 mmol) was added slowly and the solution stirred for 4 h. The reaction was poured into cold methanol (-40°C) and a yellow solid was collected by subsequent filtration(0.18, 87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 32.24H),

5.8-5.9 (s, 1H), 5.2-5.0 (m, 2H), 3.9-3.8 (m, 1H), 3.4-3.3 (m, 1H), 2.5-2.4 (m, 2H), 1.8-1.1 (m, 32.09).

Soluble Tin Chloride Ether Polystyrene 3-13

Soluble allyl ether polystyrene (2g, 1.66 mmol) and dibutyltindichloride (1.5g, 5.0 mmol) were dissolved in distilled benzene and stirred at room temperature under an atmosphere of argon. Dibutyltindihydride was slowly dripped in and the solution was irradiated for 12 h. The reaction was poured into cold methanol (-40°C) and the remaining grey solid was recovered by vacuum filtration and dried under vaccum (0.103, 0.53%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 48.1H), 3.4-3.2 (m, 4H), 2.5-2.4 (s, 1H), 1.8-0.8 (m, 86.7H).

Soluble Allyl Tin Polystyrene 3-14

Soluble tin chloride ether polystyrene (1.4g, 1.16 mmol) dissolved in distilled THF. A solution of allyl magnesium bromide (7ml, 1M) was added at room temperature and the solution was stirred at reflux for 12 h. The reaction was poured into cold methanol. Filtration and drying under vacuum yielded a grey solid (0.05 g. 0.11%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.1-6.2 (m, 18.3), 6.0-5.9 (s, 1H), 5.1-4.8 (m, 2H), 3.5-3.3 (m, 2H), 2.5-2.4 (s, 2H), 1.8-1.0 (m, 28.5H).

Polystyrene Supported Benzyl Alcohol 4-2

A mixture of the polystyrene supported benzyl chloride (6 g, 16.2 mmol), potassium acetate (20 g, 204 mmol), and tetrabutylammonium bromide (6 g, 18.6 mmol) was stirred at reflux for a period of 8 h. Potassium hydroxide(17.3 g, 308 mmol) was then added and the solution continued to stir at reflux for 12 hours. The milky white solution was slowly poured into methanol previously cooled to -78^0C, and the precipitate was collected through vacuum filtration to give white solid (6.69 g, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz) ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 12H), 4.6-4.4 (s, 2H), 1.9-1.2 (m, 8.4H).

Polystyrene Supported α-bromo ester 4-3

A solution of the polystyrene supported benzyl alcohol (5.7 g, 15.7 mmol), dicyclohexylcarbodiimide (4.8 g, 23.5 mmol), and dimethylaminopyridine(0.7 g, 6.3 mmol), was stirred at 0°C in 30 ml CH_2Cl_2. Bromoacetic acid (4.4 g, 31.3 mmol) dissolved in 10 ml methylene chloride was then slowly added. The subsequent solution was allowed to warm to room temperature and stirred an additional 1.5 h. The yellow mixture was poured into methanol at –78°C and the precipitate was collected by vacuum

filtration (8.56 g, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3-6.2 (m, 12H), 5.2-5.0 (s, 2H), 3.9-3.7 (s, 2H), 1.8-1.2 (m, 10.6H). GPC (Mn=15307. Disp=1.889)

Polystyrene Supported Pentenoic ester 4-14

A solution of the α-bromo ester (2g, 5.4 mmol), allyltributyltin (5ml, 16.2 mmol), and AIBN (10 mg) was degassed with argon for ten minutes and stirred in 30 ml dry benzene for 12 h. The solvent was then concentrated under reduced pressure with no heat, and was poured into cold methanol to induce precipitation. A light yellow solid was recovered upon vacuum filtration (2.07 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 19.7H), 5.9-5.7 (s, 1H), 5.1-4.9 (m, 2H), 2.4-2.2 (s, 2H), 1.8-0.9 (m, 10.3H)

Pentenoic Acid (4-6)

A mixture of polystyrene supported pentenoic ester (1.1 g, 1.9 mmol), lithium hydroxide(1.0 g, 29.7 mmol), and tetrabutylammonium bromide (0.6 g, 1.9 mmol) was stirred in a mixture of THF/H_2O (3:1) at reflux for 12 h. The white solution was extracted two times with diethyl ether, and the aqueous layer was then acidified with 3M HCl until pH of one was attained. The aqueous layer was extracted with ethyl acetate four times and the organic layer was concentrated under reduced pressure. Crude mixture was diluted with diethyl ether. Orange precipitate separated by filtration and pure yellow

oil was collected upon concentration. (158 mg, 84%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.2 (s, 1H), 5.8 (m, 1H), 5.0 (m, 2H), 2.3 (m, 4H); ^{13}C NMR 179.4, 136.2, 115.5, 32.2, 28.3. This compound is commercially available from Aldrich.

Polystyrene Supported Methyl Pentenoic Ester 4-5

Polystyrene supported δ-bromo ester (3g, 8.3 mmol) was added to solution of methallyltributyltin (3.6 g, 24.9 mmol), and AIBN (10 mg) in 125 ml of freshly distilled benzene. The solution was degassed with argon for ten minutes and was stirred at reflux for 12 h. The solvent was concentrated under reduced pressure and poured into cold methanol. White precipitate was collected by vacuum filtration (2.8 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 18H), 5.0 (s, 2H), 4.6 (d, 2H), 2.6-2.2 (m, 4H), 1.8-0.8 (m, 22H). GPC (Mn=10461. Disp=2.155)

4-methyl-4-Pentenioc Acid (4-7)

Polystyrene supported methyl pentenoic ester (1 g, 1.8 mmol) was added to a solution of lithium hydroxide (1g, 30 mmol), and tetrabutylammonium bromide (1.1 g, 30 mmol) in a mixture of 50 ml of THF/H_20. The mixture was stirred at reflux 12 h. The solvent was then concentrated under reduced pressure and extracted with ether. The aqueous layer was then separated and acidified with 3M HCl until a pH of one was

attained. The aqueous layer was re-extracted with ethyl acetate (4 x 30ml). The solvent was then concentrated to give yellow oil. (143 mg, 70%) Spectral data was identical to that reported by Negishi and Coperet.[92] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.6 (s, 1H), 4.8 (s, 2H), 2.5 (m, 2H), 2.3 (m, 2H), 1.7 (s, 3H); ^{13}C NMR δ 180.0, 143.6, 110.4, 32.4, 32.1, 22.4; IR (NaCl) 2955.3 , 1713.7, 1643.2.

5-Benzyloxy methyl-2,2-dimethyl-tetrahydro-furo [2,3,*d*][1,3] dioxol-6-ol 4-9

Sodium hydride (60% in mineral dispersion, 2.7g, 68.45 mmol) was placed in an oven dried 250 ml round bottom flask purged with argon. The sodium hydride was washed with pentane (3 X 20 ml) to remove the mineral oil coating and was diluted with 90 ml dry THF. The sugar diol (10.85g, 57.0 mmol) was dissolved into minimal amount of freshly distilled tetrahydrofuran. The sugar diol solution was added slowly via syringe to the sodium hydride solution which was cooled to –78°C. After gas liberation was complete tetrabutylammionium iodide (10.52g, 28.5 mmol) was added to the stirring solution. Benzyl bromide (7.11 ml, 59.85 mmol) was then added to the solution by syringe, and the solution was allowed to warm to room temperature. The reaction was complete after 2.5 h. The reaction was then extracted with ethyl acetate (3 X 30 ml), and the resultant organic layer was dried over magnesium sulfate. The filtered solution was concentrated under reduced pressure and submitted to flash column chromatography to yield compound **2** (8.8g, 55%). R_f 0.6 (35% THF/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 6.0 (d, *J*=3.8 Hz, 1H), 4.65 (d, *J*=3.8 Hz), 4.60(center of AB q, *J*=9.0 Hz,

2H), 4.29 (q, J=3.8 Hz, 1H), 4.01 (d, J=3.4, 1H), 3.90 (dd, J=5.2, 4.7 Hz, 2H), 1.49 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 137.25, 128.65, 128.28, 127.84, 111.88, 105.18, 82.76, 82.57, 80.34, 72.02, 61.00, 26.93, 26.43; IR (NaCl) 3460.8, 1214.4, 1079.2, 1014.6. Anal Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.17.

2-Bromo propionic acid 5 benzyloxymethyl-2,2-dimethyl-tetrahydro-furo[2,3,*d*][1,3]d ioxol-6-yl ester 4-10

Dicyclohexylcarbodimide (4.42g, 21.4 mmol) was dissolved in freshly distilled methylene chloride (138 ml) in an oven dried 500 ml round bottom flask purged with argon. α-Bromopropenoic acid (2.17 ml, 24.14 mmol) was added via syringe and then cooled to 0°C for 30 min. In a separate flask, compound **4-9** (4.0g, 14.2 mmol) was dissolved in freshly distilled methylene chloride (100 ml) with a catalytic amount of N,N-Dimethyl-4-pyridinamine (700mg, 5.7 mmol). The solution of compound **4-9** was added via syringe to the DCC/acid solution at 0°C, and allowed to warm up to room temperature. The reaction was complete in 30 min. The solution was concentrated under reduced pressure and then redissolved in a 1:1 mixture of methyene chloride/hexane. The white precipitate was then separated by gravity filtration. The solvent was concentrated and the crude mixture was purified by flash chromatography to give compound **4-10** (5.80g, 98%). R_f 0.20 (35% THF/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.97 (d, J=3.8 Hz, 1H), 4.64 (d, J=3.8 Hz, 1H), 4.60 (center of AB q, J=2 Hz), 4.39 (complex m, 4H), 4.01 (d, J=3.3 Hz), 1.81 (dd, J=3.4,3.4 Hz, 3H), 1.5 (s, 3H),

1.33(s,3H).^{13}CNMRδ 170.18,137.25,128.73,128.61, 127.99, 112.12, 105.44, 82.24, 77.86 72.16, 63.74, 39.93, 26.99, 21.75; IR (NaCl) 1742.7, 1072.9, 732.1. Anal Calcd for $C_{18}H_{20}O_5$ C, 52.06; H, 5.58. Found: C, 52.36; H, 5.68.

2-methyl-pent-4-enoic acid 5 benzyloxymethyl-2,2-dimethyl-tetrahydro-furo[2,3,*d*][1,3]d ioxol-6-yl ester 4-11

Compound **4-10** (100mg, 24.08 mmol) and zinc chloride (32.87 mg, 0.2408 mmol) were dissolved in a mixture of freshly distilled 4:1 CH_2Cl_2/THF (0.5 ml). Allyltributyltin (370 mg, 1.204 mmol) and triethylborane (1M in hexane) (1 ml, 1 mmol) were added to the solution which was cooled to –78°C. Five milliliters of oxygen was added via syringe over 2 min. The reaction was kept at –78°C until judged to be complete by TLC (35% THF/Hex) at approximately two hours. The reaction was extracted with ether (20 ml) and washed with brine (3 X 10 ml). The concentrate was dried over magnesium sulfate and finally purified by flash chromatography to yield compound **4-11** (80 mg, 89%). R_f 0.23 (35% THR/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.96 (d, *J*=3.8 Hz, 1H), 5.73 (m, 1H), 5.01 (t, *J*=13.1 Hz, 1H), 4.64 (d, *J*=3.8 Hz, 1H), 4.59 (center of ab q, *J*=11.9 Hz, 2H), 4.39 (m, 3H), 3.99 (d, *J*=2.5 Hz, 1H), 2.49 (complex m, 2H), 2.19 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H), 1.15 (dd, *J*=1.9, 1.9 Hz, 3H); ^{13}C NMR δ 175.97, 137.32, 128.68, 128.17, 127.83, 117.13, 111.95, 105.34, 82.22, 81.79, 78.31, 76.27, 72.05, 62.24, 39.18, 39.09, 37.84, 26.94, 16.63; IR (NaCl) 3072.0, 1736.9, 1637.0, 1078.7. Anal Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.25; H, 7.62.

2-Methyl-4-pentenoic acid (4-12)

Compound **4-11** (230mg, .06109 mmol) was added to a 10 ml round bottom flask with 1.5 ml of a 5:1 THF/H_2O mixture. To a solution of lithium hydroxide monohydrate (255mg, 6.109 mmol) and tetrabutylammonium bromide (295mg, 0.9163 mmol) was added and allowed to stir at room temperature for 12 h. The reaction was extracted with ethyl acetate (3 X 10ml), and washed with water. The cleaved sugar was recovered from the ethyl acetate. The resultant aqueous layer was then acidified with a 1 M solution of HCl, and re-extracted with ethyl acetate (3 X 10ml). The resultant organic phase was dried over magnesium sulfate and then concentrated to give compound 5 (6.9 mg, 70%). Spectral data was identical to that reported by Silverstein and Riley.[70] R_f 0.69 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.8 (s, 1H), 5.7 (m, 1H), 5.0 (m, 2H), 2.6-2.2 (m, 3H), 1.2 (d, 3H, *J*=6Hz); ^{13}C NMR δ 182.86, 134.99, 117.023, 39.05, 37.34, 16.12; IR: (NaCl) 1708, 1643.

Sugar mounted polymer 4-13

Chloro-polymer **2-9** (2.96 mmol/g, 2.3g, 6,8 mmol) was dissolved in 12 ml of DMA. NaH (60% in mineral oil, 0.44g, 10.8 mmol) was washed with pentane twice, and 4 ml of DMA was added and cooled to −30°C. A solution of 1,2-o-isopropylidene-D-

xylofuranose (2g, 10.6 mmol) in 12 ml of DMA was slowly transferred into above NaH suspension at –30°C with a syringe. After transfer was complete, the mixture was stirred for 30 min at room temperature to make sure no further hydrogen was released. The deprotonated mixture was transferred into the prepared polymer solution. The reaction was stirred for 10 h. The reaction solution was poured into 200 ml of methanol at –78°C with agitation to obtain the sugar mounted polymer **4-13**. It was filtered, washed with methanol, and dried by full vacuum pump (2.9 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.1 (m, 17H), 5.98 (s, 1H), 4.8-4.3 (m, 3H), 4.2 (s, 1H), 3.8 (m, 3H), 2.0-0.9 (m, 20H).

Bromo-ester polymer 4-14

Sugar mounted polymer **4-13** (1.7 mmol/g, 1g, 1.7 mmol) and 4-dimethyl aminopyridine (0.08g, 0.68 mmol) was dissolved in 10 ml of methylene chloride. To a solution of N-N'-dicyclohexyl-carbodiimide (0.63g, 3.1 mmol) in 16 ml of methylene chloride was added 2-bromopropionic acid (0.31g, 3.5 mmol) at –30°C. The mixture was stirred for 30 min. The above prepared polymer solution was added at –30°C. The mixture was stirred for 6-8 hr at room temperature. The white urea precipitate was removed by filtration. The filtrate was poured into methanol at –78°C to obtain bromo-ester polymer (3). The solid was filtered, washed with methanol and dried by full vacuum pump to give 1.2g. (27%, 1.4 mmol/g) ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.2-6.1

(m, 17H), 5.98 (s, 1H), 4.8-4.5 (m, 3H), 4.2 (m, 4H), 3.9 (s, 1H), 1.8 (s, 3H), 1.6-0.9 (m, 14H)

Allylated polymer 4-15

To a solution of bromoester polymer **4-14** (1.38 mmol/g, 0.4g, 0.55 mmol) in benzene (8 ml) was added AIBN (0.28g, 1.7 mmol) and allyltributyltin (2 ml, 5.5 mmol). The solution was stirred at 80°C for 14 h. The reaction was poured into –78°C methanol to precipitate the allylated polymer **4-15**. It was filtered, washed with methanol and dried by full vacuum pump (0.35g, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.1 (m, 20H), 5.98 (s, 1H), 5.70 (m, 1H), 5.0 (m, 2H), 4.5 (m, 6H), 3.9 (s, 1H), 2.58 (s, 1H), 2.38 (s, 1H), 2.15 (s, 1H), 1.8-0.9 (m, 16H), 1.1 (s, 3H)

2-methyl-4-Pentenoic acid (4-12)

Allylated polymer **4-15** (1.4 mmol/g, 0.35g, 0.5 mmol) was dissolved in THF:H_2O (9:1, 20 ml). The flask was sealed and solution was purged with nitrogen. To this solution was added H_2O_2 (30%, 1.15 ml, 12 mmol) followed by addition of LiOH solution (0.27g in 2 ml of distilled water, 6.4 mmol). The mixture was stirred for 6-8 hr at reflux. The two layers were separated by extractions. The organic layer was concentrated to reduce solvent, then poured into methanol at –78°C to obtain sugar polymer **4-13.** The

sugar auxiliary content was determined as 24% by ^{1}H NMR according to the peak (a) on sugar ring; 1.57 mmol/g. The filtrate was evaporated, 6 N HCl was added and the solutions was extracted with ethyl acetate, dried on anhydrous $NaSO_4$, and evaporated to give compound **4-12** (30mg, 89%). Spectral data was identical to that reported by Silverstein and Riley.[70] R_f 0.69 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.8 (s, 1H), 5.7 (m, 1H), 5.0 (m, 2H), 2.6-2.2 (m, 3H), 1.2 (d, *J*=6Hz, 3H); ^{13}C NMR δ 182.86, 134.99, 117.023, 39.05, 37.34, 16.12; IR: (NaCl) 1708, 1643.

5-Norbornene-2-Methanol (5-5)

5-Norbornene-2-carboxaldehyde (10g, 82 mmol) and sodium borohydride (9.3g, 24.6 mmol) was stirred at 25°C for 5 minutes under an atmosphere of argon. Thin layer shows complete conversion of starting material to product. The reaction was quenched with water and extracted with ether four times. The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The product was purified under flash chromatography to give compound **5-5** (9.2g, 92%). This compound is commercially available from Aldrich. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.2-5.9 (m, 2H), 3.7-3.2 (m, 2H), 2.9-2.7 (m, 2H), 2.3 (m, 1H), 1.8 (m, 1H), 1.6 (m, 1H), 1.4-1.1 (m, 3H); ^{13}C NMR δ 136.93, 136.40, 136.23, 132.01, 66.72, 66.74, 49.22, 44.65, 43.32, 43.03, 41.95, 41.36, 41.26, 41.20, 29.34, 28.62.

5-Norbornene-2-Bromo Propionate 5-7

5-Norbornene-2-methanol **5-5** (3g, 24.2 mmol) was added to a solution of DCC (9.9g, 48.4 mmol) and DMAP (1.5g, 9.68mmol) in freshly distilled methylene chloride (80mL). The solution was cooled to 0°C and bromo propionic acid (7.4g, 48.4) was slowly added. The reaction was stirred 1h cold and then allowed to stir at room temperature for an additional 2h. Urea was filtered by gravity filtration and the resulting solution was concentrated under reduced pressure. The crude material was purified by flash chromatography to give compound **5-7** (5.9g, 89%). R_f 0.77 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ **6.4–6.0** (m, 2H), 4.5 (q, *J*= 7.02 Hz, 1H), 4.4-3.8 (m, 2H), 3.1 (m, 2H), 2.6 (m, 1H), 2.0 (m, 4H), 1.6-1.4 (m, 2H), 0.2 (m, 1H).). ^{13}C NMR δ 169.81, 137.44, 137.37, 136.71, 131.95, 131.88, 68.97, 49.13, 44.75, 43.56, 43.34, 41.96, 41.38, 40.13, 40.06, 37.37, 29.24, 28.62, 21.46. IR(NaCl) 2966, 1736, 1443. Anal. Calcd for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C: 50.61, 6.16.

ROMP-Supported 2-Bromo-2-Propionate Ester 5-9

5-Norbornene-2-bromo propionate **5-7** (1g, 3.12mmol) was dissolved in 1.5 mL dry CH_2Cl_2. Grubbs catalyst (5mg) was added under argon and the reaction was allowed to stir for 60s at which point the reaction mixture became top thick to stir well. Ethyl vinyl ether was added to cap the polymerization, and the solution was poured into methanol at room temperature. The polymer was extracted from solution and dried under

full pump to give a white solid **5-9** (0.467g, 47%) ^{1}H NMR ($CDCl_3$, 300 MHz) 5.4 (s, 2H) 4.4 (s, 1H), 4.2-3.9 (m, 2H), 3.0-1.5 (complex m, 10H), 1.3-1.0 (s, 1H). GPC (Mn=36045. Disp=2.647)

ROMP-Supported 2-Methyl-4-Pentenoate Ester 5-11

ROMP-Supported 2-Bromo-2-Propionate Ester **5-9** (0.5g, 1.94mmol) was dissolved in freshly distilled benzene (60mL) and added to AIBN (10mg), and allyltributyltin (7.2mL, 2.34mmol). The solution was stirred at reflux for 13 h and then cooled to room temperature. The solvent was concentrated under reduced pressure and poured into methanol which precipitated a yellow solid. The solid was then washed with methanol and dried under vacuum to give the polymer **5-11** (0.406g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.8 (m, 1H), 5.4 (m, 4H), 5.0 (m, 2H), 4.2-3.8 (m, 5H), 2.8-1.2 (m, 7H).

2-Methyl-4-Pentenoic Acid (5-13)

ROMP-Supported 2-Methyl-4-Pentenoate Ester **5-11** (0.16g, 0.77mmol), lithium hydroxide(0.2g, 8.3mmol) was dissolved in 50mL of THF/H_2O mixture (1:1). The solution was stirred at 70^{0}C for 12h and then cooled to room temperature. The solution was extracted with ether, and the aqueous layer was subsequently acidified with 3M HCl

until a pH of 1 was attained. The aqueous layer was extracted with ethyl acetate 4X. The organic fraction was concentrated to give yellow oil. Purification was completed using flash chromatography with 5 drops of acetic acid per 100 mL of elluent. The product was isolated as a colorless oil (46 mg, 87%). Spectral data was identical to that reported by Silverstein and Riley.[70] R_f 0.69 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.8 (s, 1H), 5.7 (m, 1H), 5.0 (m, 2H), 2.6-2.2 (m, 3H), 1.2 (d, 3H); ^{13}C NMR δ 182.86, 134.99, 117.023, 39.05, 37.34, 16.12; IR: (NaCl) 1708, 1643.

ROMP-Supported Propionate ester 5-15

To a solution of ROMP-Supported 2-Bromo-2-Propionate Ester **5-13** (0.5g, 1.94 mmol) and AIBN (mg) dissolved in 50 mL of dry benzene was added tributyltinhydride (0.63 mL, 2.34 mmol) and the solution was stirred at reflux for 4h. An additional equivalent of tributyltinhydride (0.52 mL, 1.94 mmol) was added, and the solution was stirred at reflux for an additional 4 h. The solvent was concentrated under vacuum until white precipitate was evident, and methanol was poured in and stirred at room temperature. A white/green precipitate was extracted from the mixture, washed with excess methanol, and dried under vacuum (0.35g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.2 (s, 2H), 4.0 (m, 2H), 3.0-1.0 (m, 12H).

5-Norbornene-2-(2-bromo-2-phenyl acetate) 5-8

5-Norbornene-2-Methanol **5-5** (3g, 24mmol) was slowly added to a solution of 2-bromo-phenylacetic acid (7.7g, 36mmol), dicyclohexylcarbodiimide (7.4g, 36mmol), and dimethylaminopyridine (1.1g, 0.9mmol) dissolved in freshly distilled methylene chloride. The solution was stirred at room temperature for 5 h and filtered. The filtrate was concentrated under reduced pressure to give a thick yellow oil. The crude oil was purified with flash chromatography and a thick colorless oil was recovered (6.25g, 78%). R_f 0.59 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8-7.4 (m, 5H), 6.3-6.0 (m, 2H), 5.4 (d, 1H, *J*=5.5 Hz), 4.4-3.9 (m, 2H), 3.0-2.6 (m, 2H), 2.0 (complex m, 5H). ^{13}C NMR δ 168.09, 137.59, 136.86, 135.99, 135.80, 132.01, 129.17, 128.71, 128.58, 69.71, 49.27, 47.06, 46.92, 44.91, 43.70, 42.10, 41.52, 37.76, 37.51, 29.38, 28.72. IR (NaCl): 1746, 1703. HRMS (CI) calcd for $C_{16}H_{17}O_2$ 321.0490, found 321.0502.

ROMP-Supported 2-bromo-2-phenyl acetate 5-10

Grubbs catalyst (5 mg) added to a solution of 5-Norbornene-2-(2-bromo-2-phenyl acetate **5-8** (0.322g, 1.0 mmol) in methylene chloride (0.3 mL). The solution was stirred for 30 seconds until it became very viscous. Allyl vinyl ether (1mL) was added and the solution was poured into methanol. The orange precipitate was extracted from the mixture, washed with methanol, and dried under vacuum (0.293g , 91%). ^{1}H NMR

($CDCl_3$, 300 MHz) δ 7.4 (m, 5H), 5.2 (m, 3H), 4.0 (m, 2H), 2.8-2.2 (m, 2H), 2.0-1.6 (m, 3H), 1.0 (s, 2H). ^{13}C NMR δ 168.10, 137.60, 135.73, 132.00, 129.17, 128.72, 128.61, 69.69, 49.25, 47.04, 46.89, 43.67, 42.07, 41.30, 37.47, 28.70. GPC (Mn=23689. Disp=2.628)

ROMP-Supported 2-Phenyl-4-Pentenoate Ester 5-12

A solution of ROMP-Supported 2-bromo-2-phenyl acetate **5-10** (0.58g, 1.8mmol), Allyltributyltin (1.7mL, 5.43 mmol), AIBN (10mg) in dry benzene (50 mL) was degassed under argon for 20 minutes. The solution was then stirred at reflux for 12 h under an atmosphere of argon. The solution was cooled to room temperature, and concentrated under reduced pressure with no heat applied. The crude mixture was poured into methanol at room temperature which induced precipitation of a white/grey solid. The solid was extracted from the mixture and dried under vacuum for 12 h (0.35g, 85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2 (m, 5H), 5.7 (1H), 5.2-5.0 (m, 4H), 4.1-3.8 (m, 2H), 3.5 (m, 2H), 2.8 (m, 1H), 2.5 (m, 1H), 2.0 (m, 2H), 1.4 (m, 2H), 1.2 (m, 2H). GPC (Mn=25528. Disp=2.237)

2-Phenyl-4-Pentenioc Acid (5-14)

A solution of ROMP-Supported 2-Phenyl-4-Pentenoate Ester **5-12** (0.25g, 0.93mmol), lithium hydroxide (0.22g, 9.3mmol) was dissolved in a mixture of 50 mL THF/H_2O (1:1). The solution was stirred at 70° for 18 h. The mixture was then concentrated and diluted with ethyl ether. The aqueous layer was carefully acidified with 3M HCl until a pH of 1 was attained. This aqueous layer was then extracted with ethyl acetate 5X. The solvent was concentrated under reduced pressure, and the crude mixture was purified using column chromatography with 5 drops of acetic acid per 100 mL of elluent. The product was collected as a colorless oil (125 mg, 76%). Spectral data reported is identical to that reported by Padwa and co-wrokers.[93] R_f 0.55 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.7 (s, 1H), 7.3 (m, 5H), 5.7 (m, 1H), 5.1 (m, 2H), 3.6 (dd, 1H, 7.3, 7.0 Hz), 2.82 (m, 1H), 2.5 (m, 1H). ^{13}C NMR δ 179.0, 137.2, 134.2, 128.1, 127.5, 126.9, 116.3, 50.9, 36.4

ROMP-Supported 2-phenyl-actate 5-16

To a solution of ROMP-Supported 2-bromo-2-phenyl acetate **5-10** (0.35g, 1.09 mmol) and AIBN (10 mg) dissolved in dry benzene (30 mL) was added tributyltinhdride (0.87 mL, 3.27 mmol). The solution was degassed with argon for 10 minutes and stirred at reflux under an atmostphere of argon for 12 h. The solution was then cooled and concentrated under reduced pressure with no heat. The crude mixture was slowly poured into methanol at room temperature and a white/grey precipitate was collected and dried under vacuum for 8 h (0.261g, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (M, 5H), 5.2 (m, 2H), 4.0(d, 2H), 3.5 (m, 2H), 2.0-1.0 (m, 7H). ^{13}C NMR

δ171.93, 134.56, 129.70, 128.94, 127.44, 66.99, 41.90, 36.93, 31.06, 27.91, 14.15, 10.38. GPC (Mn=25179. Disp=2.773)

2-phenyl acetic acid (5-17)

To a solution of ROMP-Supported 2-phenyl-actate **5-16** (0.3g, 1.24 mmol) dissolved in 30 mL of a mixture of THF/H_2O (4:1) was added lithium hydroxide (0.3g, 12.4 mmol). The solution was stirred at reflux for 12 h and the solvent was concentrated under reduced pressure. 2 mL of 3M HCl was added so that a pH of 1 was attained. The mixture was extracted with ethyl acetate (5 X 40 mL) and the organic layer was dried with sodium sulfate and concentrated. The crude mixture was purified by flash chromatography to give a colorless oil (98 mg, 59%). R_f 0.45 (35% EtOAc/Hex). This compound is commercially available from Aldrich.

5,6 bis-hydroxy methyl norborn-2-ene (5-19)

A solution of lithium aluminum hydride (4.6g, 0.122mmol) and 100 freshly distilled THF was stirred at 0°C. A solution of cis-5-Norbornene-endo-2,3,dicarboxlic anhydride (10g, 61 mmol) dissolved in 125 mL freshly distilled THF was slowly added over a period of 1h. The mixture was stirred at 0°C for one hour and was then allowed to warm to room temperature. The solution was then stirred at ambient temperature for and

additional 5h. The reaction was quenched slowly with water followed by 3M HCl. The mixture was extracted with ethyl acetate 3X and the organic portion was concentrated and dried with sodium sulfate to give a white solid (7.74 g, 82%). Spectral data is identical to that reported by Wu and co-workers.[94] R_f 0.52 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.2 (m, 2H), 4.6 (s, 2H), 3.77 (dd, *J*=5.6, 9.6 Hz, 1H), 3.65 (dd, *J*=5.2, 9.6 Hz, 1H), 3.5 (t, *J*=10 Hz, 1H), 3.02 (m, 2H), 2.65 (m, 2H), 1.5 (m, 2H). ^{13}C NMR δ 134.61, 62.99, 49.69, 46.25, 44.76.

5,6 bis-(2-bromo-2-phenyl-acetate) methyl norborn-2-ene 5-20

5,6 bis-hydroxy methyl norborn-2-ene **5-19** (1.4g, 8.9 mmol) was slowly added at 0°C to a solution of dicyclohexylcarbodiimide (4.03g, 19.3mmol), dimethylaminopyridine (0.4g, 3.6 mmol), and bromo-phenyl-acetic acid (5.7g, 26.7mmol) in 25mL dry methylene chloride. The solution was stirred cold for 1 h. The urea was separated b gravity filtration, and the filtrate was concentrated to give thick yellow oil. Purification by flash chromatography gave light yellow oil (4.1g, 80%).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (d, 4H), 7.3 (d, 6H), 6.0 (m, 2H), 5.3 (s, 2H), 3.9 (m, 4H), 2.8 (d, 2H), 2.5 (s, 2H), 2.0(s,2H).^{13}CNMRδ 167.79, 167.77, 135.54, 135.47, 135.25, 129.15, 128.87,128.66, 128 .59, 128.55, 128.47, 66.27, 48.83, 46.83, 46.70, 45.15, 45.13, 40.14, 40.10. IR (NaCl): 3031, 2968, 2870, 1736, 1490, 1454. Anal. Calcd for $C_{25}H_{24}Br_2O_4$: C, 54.77; H, 4.41. Found: C, 55.11; H, 4.28.

ROMP-Supported bis-(2-bromo-2-phenyl-acetate) 5-21

5,6 bis-(2-bromo-2-phenyl-acetate) methyl norborn-2-ene **5-20** (1.81g, 3.2mmol) was dissolved in 2 mL dry methylene chloride and was stirred at room temperature under an atmosphere of argon. Grubbs catalyst (5 mg, 0.02 mol%) was added and the reaction bubbled vigorously for 30 seconds upon which the ethyl vinyl ether (2mL) was added to stop the polymerization. The solution was poured into methanol at room temperature which induced the precipitation of the polymer. The solid was extracted from the solution, washed with excess methanol, and dried under vacuum for 6h (1.32g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.6-7.2 (d, 2H), 5.4-5.1 (m, 4H), 4.2-3.9 (s, 4H), 2.8- 1.2 (complex m, 8H). ^{13}C NMR δ 167.91, 135.51, 132.07, 129.373, 128.78, 128.67, 127.24, 64.71, 46.75, 44.02, 43.39, 25.62.

ROMP-Supported bis-(2-phenyl-4-Pentenoate Ester) 5-22

To a solution of ROMP-Supported bis-(2-bromo-2-phenyl-acetate) **5-21** (0.35g, 0.61mmol), AIBN (10mg) in benzene freshly distilled was added allyltributyltin (0.57mL, 1.83mmol). The solution was degassed under argon for 20 minutes, and stirred at reflux for 12 h. The reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude mixture was poured into methanol at room temperature which induced precipitation of a white solid. The polymer was extracted

from the mixture, washed with methanol, and dried under vacuum for 6 h (0.22g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (m, 10H), 5.6 (m, 2H), 5.0 (m, 4H), 4.2-3.4 (m, 8H), 2.8-2.6 (m, 4H), 1.8-1.2 (m, 4H). GPC (Mn=10825. Disp=2.373)

ROMP-Supported bis-(2-phenyl-acetate) 5-24

To a solution of ROMP-supported bis-(2-bromo-2-phenyl-acetate) **5-21** (0.513g, 0.94 mmol) and AIBN (10mg) dissolved in 50 mL dry benzene was added tributyltinhydride (0.53 mL, 1.97 mmol). The solution was stirred at reflux for 12 h and cooled to room temperature. The solvent was concentrated under reduced pressure with no heat, and poured into methanol at room temperature. A white/grey solid was extracted from the mixture, washed with methanol, and dried under vacuum to give the reduced product (280 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (s, 10H), 5.2 (s, 2H), 4.0 (m 2H), 3.5 (s, 2H), 2.5 (m, 4H), 2.0-1.0 (m, 4H).

2-Phenyl-4-Pentenioc Acid (5-23)

To a solution of ROMP-Supported bis-(2-phenyl-4-Pentenoate Ester) **5-22** (0.1g, 0.21mmol), in 10 mL of a mixture of THF/H_2O, was added lithium hydroxide (50mg, 2.1mmol). The solution was stirred at reflux for 10 h, cooled to room temperature, and extracted with ether. The water layer was acidified with 3M HCl, and re-extracted with

ethyl acetate 4X. The organic portion was concentrated to give a dark yellow oil which was purified by flash chromatography to give a light yellow oil (28mg, 78%). Spectral data reported is identical to that reported by Padwa and co-wrokers.[93] R_f 0.55 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (s, 1H), 7.3 (m, 5H), 5.7 (m, 1H), 5.1 (m, 2H), 3.6 (dd, 1H), 2.82 (m, 1H), 2.5 (m, 1H). ^{13}C NMR δ 179.0, 137.2, 134.2, 128.1, 127.5, 126.9, 116.3, 50.9, 36.4.

2-phenyl acetic acid (5-25)

ROMP-Supported bis-(2-phenyl-acetate) **5-24** (139 mg, 0.36 mmol) and lithium hydroxide were dissolved a mixture of 1:1 THF/H_2O (25 mL). The solution was heated to reflux for 6 h. The reaction mixture was cooled to room temperature and acidified with 3M HCl until the pH ~1. The solution was extracted with ether (3 x 50 mL) and the organic layer was dried and concentrated. The crude mixture was purified through a slurry of silica gel and the product was recovered with ether containing 10 drops of acetic acid (21 mg, 67%). R_f 0.45 (35% EtOAc/Hex). This compound is commercially available from Aldrich.

2-(2-Propenyloxy)cyclohex-2-enone (6-6)

To a solution of 1,2 cyclohexanedione(5g, 44.6 mmol), and freshly distilled allyl alcohol (6.1 mL, 89.2 mmol) in benzene (89mL) freshly distilled from sodium and benzophenone was added p-toluene sulfonic acid (10 mg). The solution was stirred at reflux with a Dean-Starke tube for 12 h. The solvent was concentrated and diluted with diethyl ether. Extraction was followed with water, brine, and a saturated solution of sodium bicarbonate. The ether layer was concentrated and the crude mixture was purified by flash chromatography to give a light yellow oil (3.5g, 51%). Spectral data is identical to that reported by Ikeda and co-workers.[95] R_f 0.42 (35% EtOAc/Hex) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.0 (m, 2H), 5.4 (m, 2H), 4.4 (s, 2H), 2.5 (m, 4H), 2.0 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 193.80, 149.67, 132.40, 118.12, 117.40, 68.03, 38.37, 24.02, 22.47.

2-(Allylamino)cyclohex-2-enone (6-23)

To a solution of 1,2 cyclohexandione (5g, 44.6 mmol) and allyl amine (10.2 mL, 135 mmol) dissolved in freshly distilled benzene (70mL) was added p-toluene sulfonic acid (10mg). The solution was stirred at reflux with a Dean-Starke tube for 12 h under an atmosphere of argon. The solvent was concentrated under reduced pressure and to give a dark brown slurry. The crude mixture was purified by flash chromatography and the product was isolated from pure hexanes to 10% ether/hexanes to give a light brown oil (4.61 g, 72%). Spectral data was identical to that reported by Arnauld and co-workers.[96]

R_f 0.44 (35% EtOAc/Hex) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.7 (m, 1H), 5.3 (t, 1H), 5.0 (m, 2H), 4.2 (s, 1H), 3.4 (m, d, 2H), 2.4 (t, 2H), 2.2 (q, 3H), 1.8 (m, 2H). ^{13}C NMR($CDCl_3$, 300MHz) δ 195.27, 139.88, 134.62, 115.50, 111.11, 45.34, 37.53, 24.14, 23.13.

2- (Prop-2-enyloxy)cyclohexane-1-one (6-16)

Sodium metal (0.3g, 15 mmol) was added to freshly distilled allyl alcohol at 0°C. The solution was stirred cold for 12 min which was followed by addition of cyclohexenoxide. The resulting solution was stirred at room temperature for 1.5 h and was then stirred at reflux for 2 h. A diluted solution of sulfuric acid (3M) was slowly added until the pH was neutral. The solution was extracted with diethyl ether and washed with water and brine. The organic layer was concentrated and purified by flash chromatography to give a colorless oil (5.5g, 71%). All spectral data is identical in all respects to that of Salomon and co-workers.[97] Rf=0.27 (35:65 EtOAc:Hex). ^{1}H NMR δ 6.0 (m, 1H), 5.3 (dd, J=1.8, 17.4 Hz, 1H), 5.2 (dd, J=1.2, 10.2 Hz, 1H), 4.2 (dd, J=5.4, 12.6 Hz, 1H), 4.0 (dd, J=5.7, 12.6 Hz, 1H), 3.5 (m, 1H), 3.1 (m, 1H), 2.7 (s, OH), 2.0 (complex m, 2H), 1.7 (m, 2H), 1.3 (m, 4H), ^{13}C NMR δ 135.1, 116.9, 83.2, 73.7, 69.7, 32.0, 29.2, 24.2, 23.9. The following procedure is identical to that developed by Swern and co-workers.[98] Freshly distilled oxalyl chloride (0.53 mL, 6.2 mmol) and freshly distilled CH_2Cl_2 (5 mL) were combined under argon and cooled to -78°C. Dimethyl sulfoxide (0.44 mL, 6.2 mmol) and CH_2Cl_2 (3 mL) were combined and added dropwise to the oxalyl chloride solution, so as to keep the temperature of the solution below –60°C.

2-(2-propenoxy)cyclohexanol (440 mg, 2.8 mmol) and CH_2Cl_2 (3 mL) were combined and added dropwise to the –78°C solution. The solution was allowed to stir for fifteen minutes, after which the triethylamine (1.9 mL, 14.1 mmol) was added dropwise. The solution was then allowed to warm to room temperature. Ether (25 mL) and water (25 mL) were added to the solution. The layers were separated and the water layer was washed with ether (3 X 50 mL). The organic phases were combined and dried with sodium sulfate. The solvent was then removed under reduced pressure. The resulting crude oil was subjected to column chromatography to provide **2-57** (382 mg, 88%). Ketone **2-57** is identical in all respects to that of Salomon and co-workers.[97] ^{1}H NMR δ 5.9 (m, 1H), 5.3 (dd, *J*=1.2, 17.4 Hz, 1H), 5.2 (dd, *J*=1.2, 10.2 Hz, 1H), 4.2 (dd, *J*=5.4, 12.6 Hz, 1H), 3.9 (m, 2H), 2.5 (m, 1H), 2.2 (m, 2H), 1.9 (m, 2H), 1.8-1.6 (complex m, 3H); ^{13}C NMR δ 210.1, 134.4, 117.3, 81.7, 70.7, 40.5, 34.5, 27.6, 23.1.

2-Allyl-2-hydroxycyclohexanone (6-11)

2-allyloxy-2-cyclohexanone (190 mg, 1.25 mmol), tributyltin hydride (0.37 mL, 1.38 mmol), and AIBN (41mg, 0.25 mmol) were dissolved in benzene (2.5 mL) and degassed for 20 min with a stream of argon. The reaction mixture was then refluxed for 3h (monitored by TLC). The reaction was allowed to cool and was diluted with ether (10 mL). DBU (0.21 mL, 1.4 mmol) and 3-4 drops of water were added to the stirring solution. An ethereal solution of iodine was added dropwise until the iodine color persisted. The mixture was then filtered rapidly through silica gel with ether. The filtrate was then concentrated under reduced pressure and subjected to flash column

chromatrography to yield the Claisen rearranged product (142 mg, 74%). Alcohol **2-20** was identical in all respects to that of Mutai and co-workers.[99] ^{1}H NMR δ 5.7 (m, 1H), 5.1 (m, 2H), 4.0 (s, OH), 2.6-2.4 (complex m, 4H), 2.2 (dd, *J*=2.4, 12.6 Hz, 1H), 2.1 (m, 1H), 1.8-1.5 (complex m, 4H); ^{13}C NMR δ 213.4, 131.6, 118.7, 78.7, 41.7, 40.2, 38.2, 27.7, 22.5.

2-Propoxy-cyclohex-2-enone (6-17)

To a solution of 1,2 cyclohexanedione (2g, 17.8 mmol), and propanol (1.6 mL, 21.4 mmol) dissolved in dry benzene was added para-toluene sulfonic acid (10 mg). The solution was stirred at reflux with a Dean Starke tube for 12 h under an atmostphere of argon. The mixture was cooled to room temperature and diluted with ether. The organic phase was washed with brine followed by a saturated solution of sodium bicarbonate and the organic layer was then dried and concentrated. The crude oil was purified by flash chromatography to give a colorless oil (1.05, 38%). Spectral data is identical to that reported by Enholm and co-workers.[84] Rf=0.42 (35:65 EtOAc:Hex). ^{1}H NMR δ 5.9 (t, *J*=4.5 Hz, 1H), 3.6 (t, *J*=6.9 Hz, 2H), 2.5 (t, *J*=6.6 Hz, 2H), 2.4 (q, *J*=5.7 Hz, 2H), 2.0 (m, 2H), 1.8 (m, 2H), 1.0 (t, *J*=7.5 Hz, 3H), ^{13}C NMR δ 194.3, 150.8, 117.2, 69.1, 38.8, 24.5, 22.9, 22.0, 15.3.

2-(Diallylamino)cyclohex-2-enone (6-25)

To a solution of 1,2 cyclohexenedione (2g, 17.9 mmol) and diallylamine (2.8 mL, 23.0 mmol) dissolved in 35 mL dry benzene was added para-toluene sulfinic acid (10mg). The solution was stirred at reflux for 12 h with a Dean Starke trap under an atmosphere of argon, and the solvent was concentrated under reduced pressure. The crude oil was then purified by column chromatography and the product was recovered with straight hexane (2.3g 67%). Spectral data was identical to that reported by Meyer and co-workers.[100] R_f 0.93 (35% EtOAc/Hex) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.0 (t, 1H), 5.8 (m, 2H), 5.1 (d, 4H), 3.6 (d, 4H), 2.5 (m, 4H), 2.0 (m, 2H). ^{13}C NMR δ 196.36, 143.91, 134.24, 128.27, 116.84, 52.67, 39.33, 25.10, 22.63.

2-[N-acetyl-N-(2-propenyl)amino] cyclohex-2-enone (6-29)

To a solution of 2-(Allylamino)cyclohex-2-enone (1g, 6.63 mmol) in pyridine (32 mL) was added acetic anhydride (13.5 mL, 132.6 mmol). The solution was stirred at room temperature for 12 h. Excess reagent and solvent were concentrated under reduced pressure and the crude mixture was purified by flash chromatography (1.04g, 82%). Spectral data was identical to that reported by Ikeda and co-workers.[101] R_f 0.55 (35% EtOAc/Hex) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.7 (m, 1H), 5.5 (m, 1H), 4.9 (m, 2H), 4.2

(m, 1H), 3.5 (m, 1H), 2.4 (m, 4H), 1.9 (m, 2H), 1.6 (s, 2H). ^{13}C NMR δ 194.59, 169.59, 148.71, 139.07, 132.96, 117.20, 49.59, 37.82, 23.36, 21.89, 21.19.

2-Allyl oxy-cyclohex-2-enone *O* benzyl-oxime 6-32

To a solution of 2-(2-Propenyloxy)cyclohex-2-enone (0.1g, 0.65 mmol), and pyridine (0.26 mL, 3.3 mmol) dissolved in freshly distilled methylene chloride (1.3 mL) was added O-Benzylhydroxylamine hydrochloride (0.2g, 1.3 mmol). The solution was stirred at room temperature for 2 h. The crude reaction was then concentrated under reduced pressure and the yellow crude liquid was purified by column chromatography. A colorless liquid was collected (0.085 g, 53%). R_f 0.89 (35% EtOAc/Hex) ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5 (m, 5H), 6.2 (m, 1H), 5.5 (m, 2H), 5.4 (m, 3H), 4.6 (d, 2H), 2.9 (t, 2H), 2.4 (q, 2H), 1.9 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 151.89, 148.02, 137.54, 133.52, 128.16, 128.10, 127.63, 117.04, 107.81, 76.26, 68.48, 23.99, 23.44, 21.08. IR (NaCl): 1631, 1584, 1454. HMRS (CI) calcd for $C_{16}H_{19}O_2$ 258.1494, found 258.1483.

2-(3-Butenyl)-2-cyclohexenenone (6-35)

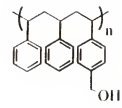
2,2,dimethyl hydrazine (15 mL, 0.198 mmol) was added to a solution of 7-Oxabicyclo[3.1.0] hexane-2,4-dione(5g, 0.446 mmol) dissolved in dry benzene (100 mL). The solution was stirred at 0°C for 45 minutes and the color turned yellow and

cloudy. The solvent was concentrated under reduced pressure. An additional amount of benzene was added (2 x 50 mL) with further concentration on the roto-vap to remove excess water. The mixture was used crude for the following reaction:

A solution of 1,4 butenyl bromide was prepared as follows: bromobutane(5g, 37.0 mmol) was slowly added to a solution of magnesium (8.9g, 370 mmol) and iodine (10 mg) in freshly distilled THF (30mL). The orange solution was allowed to stir for 2 h, and eventually turned an olive green color. To a solution of the crude mixture as prepared from above (5g, 32.0 mmol) dissolved in freshly distilled THF (64 mL), was added a solution of 1,4 butenyl magnesium bromide (29mL, 1.23 M) at 0^0C. The solution was allowed to stir at room temperature for 14 h. The solvent was then concentrated and the crude oil was diluted with a mixture of ethanol/water (10mL, 1:1). A 3M solution of HCl (3M) was added and the solution was stirred at reflux for 12 h. The ethanol was concentrated under reduced pressure and the mixture was extracted with ether (3 X 50 mL), washed with brine followed by a saturated solution of sodium bicarbonate. The organic layer was dried with sodium sulfate and concentrated under reduced pressure (1g, 21%). Spectral data was identical to that reported by Dauben and co-workers.[102] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.7 (t, 1H), 5.7 (m, 1H), 5.0 (m, 2H), 2.5-2.3 (m, 6H), 2.2 (m, 2H), 2.0 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 199.44, 145.52, 138.92, 138.14, 114.76, 38.51, 32.63, 28.93, 25.99, 23.08.

APPENDIX
SPECTRAL DATA

The ^{1}H NMR spectra of selected compounds reported in chapters 4 and 5 are illustrated in this appendix. The spectra along with the proposed structure are shown.



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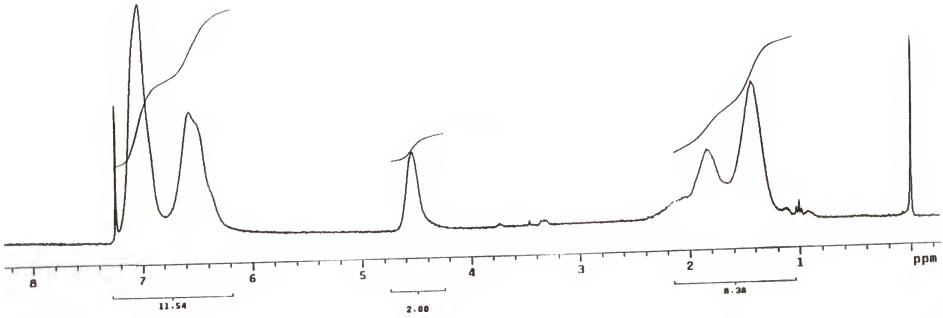

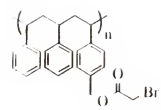

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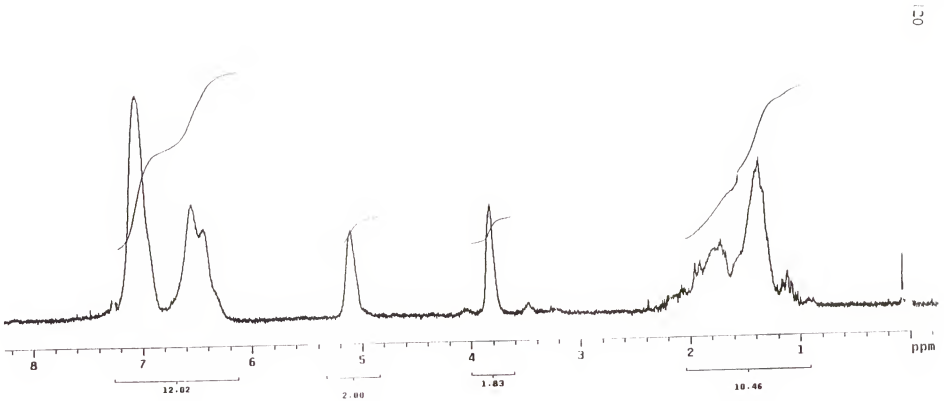
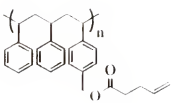
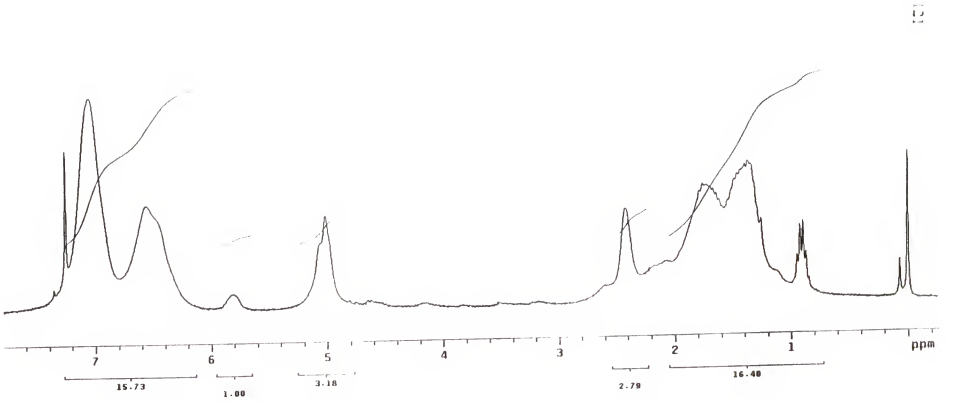
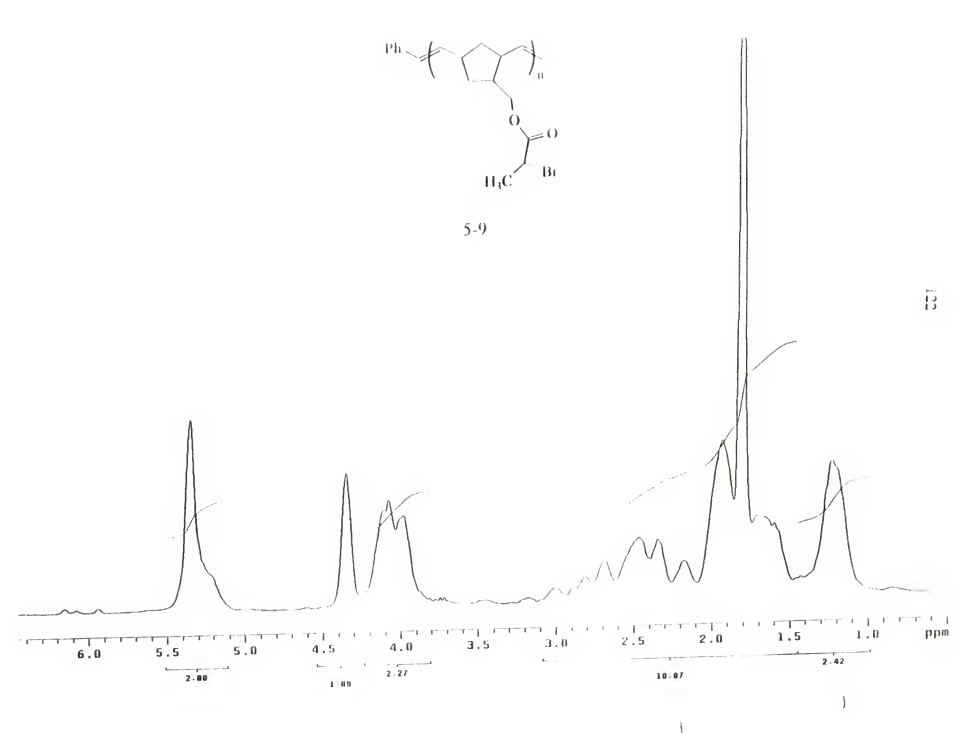




4-1

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Br
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5.0
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4.0
3.5
3.0
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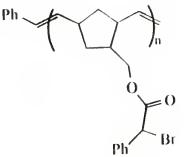
2.0
1.5
1.0
ppm
2.00
1.89
2.27
10.07
2.42

5-9



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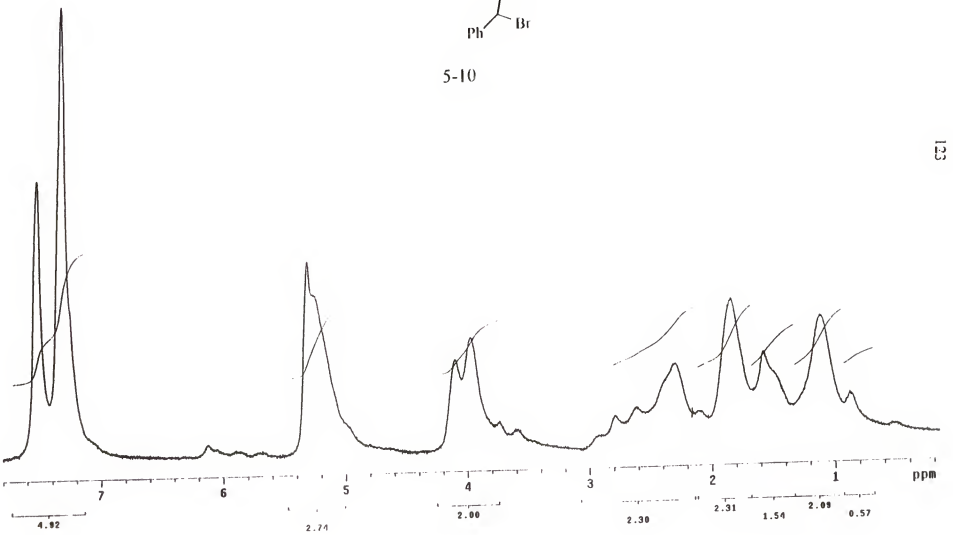

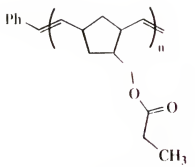

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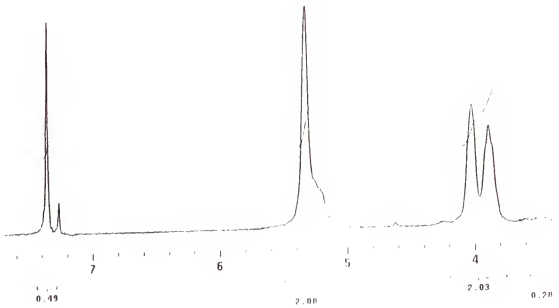
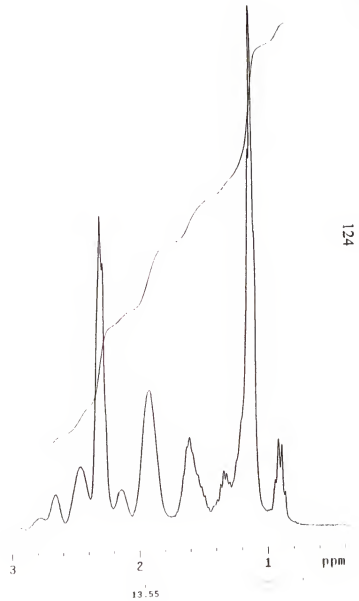
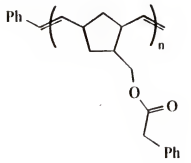
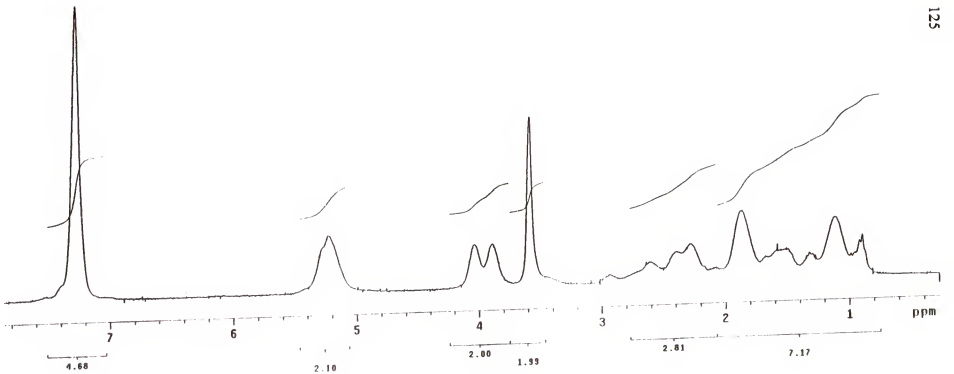
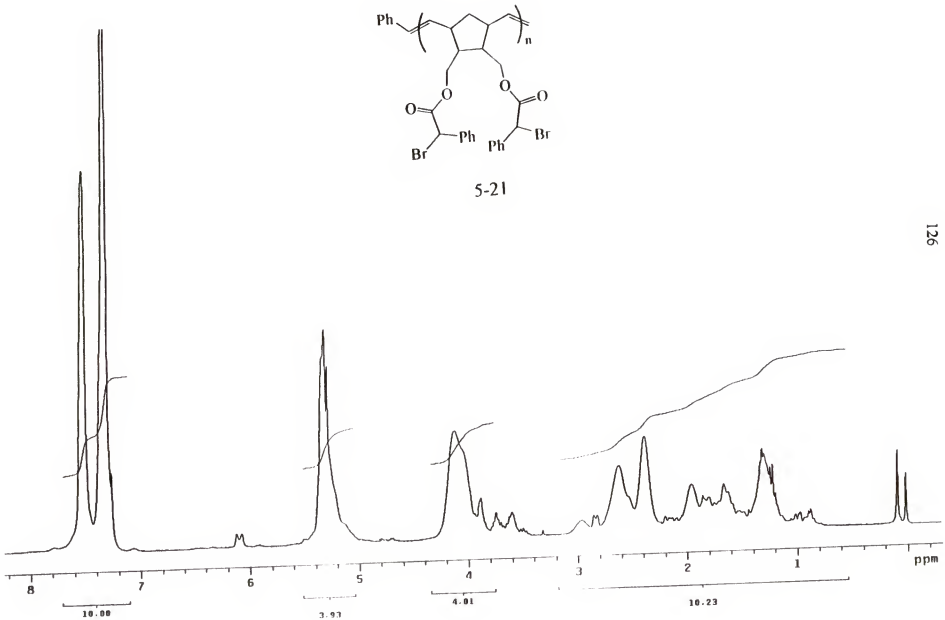






5-16





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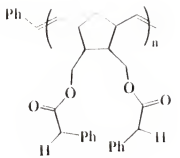
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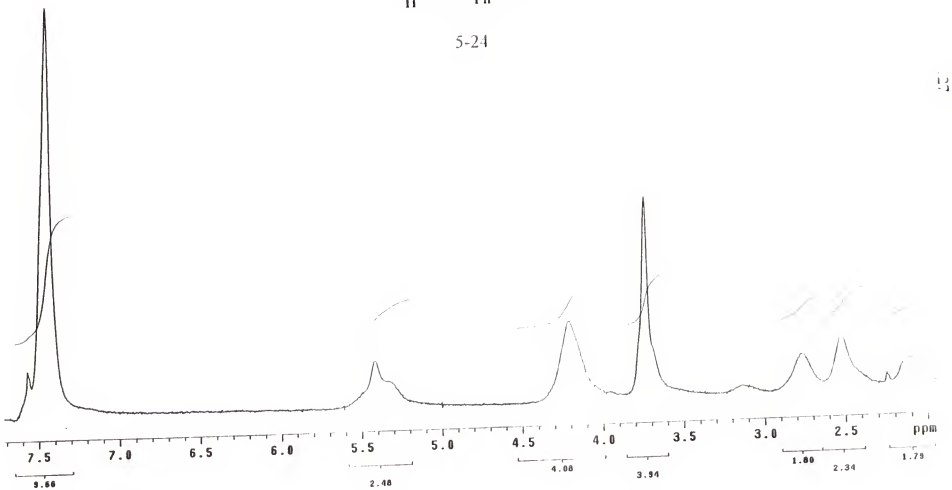
H
Ph
Ph
H

5-24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4.5
4.0
3.5
3.0
2.5
ppm
9.66
2.48
4.08
3.94
1.80
2.34
1.79

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BIOGRAPHICAL SCETCH

Maria–Elena Gallagher was born in Philadelphia but was raised in several places. Her most memorable time was in Puerto Rico where she learned another language and culture. She went to College of the Holy Cross for her undergraduate studies focusing on biology as her major course of study. She changed her focus to chemistry her first year after studying the first semester of organic chemistry. She knew early in her undergraduate career that synthetic organic chemistry most suited her interest, and decided to continue her studies in graduate school.

Maria joined Dr. Eric Enholm's group at the University of Florida studying various methods of organostannane chemistry. Along with her peers, she learned an ample amount of organic chemistry ranging from bond energies to distillation techniques in the lab. She found her graduate school experience both challenging and rewarding.

Upon completion of her Doctor of Philosophy, Maria plans to work for CB Research and Development where she will be exposed to a variety of synthetic reactions with the goal of broadening her knowledge of chemistry.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric J. Enholm, Chair
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Martin Vala
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Charles J. Allen
Professor of Biochemistry
And Molecular Biology

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

October, 2000

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Dean, Graduate School